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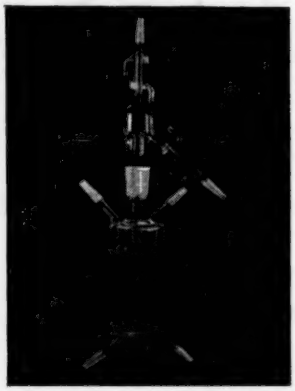

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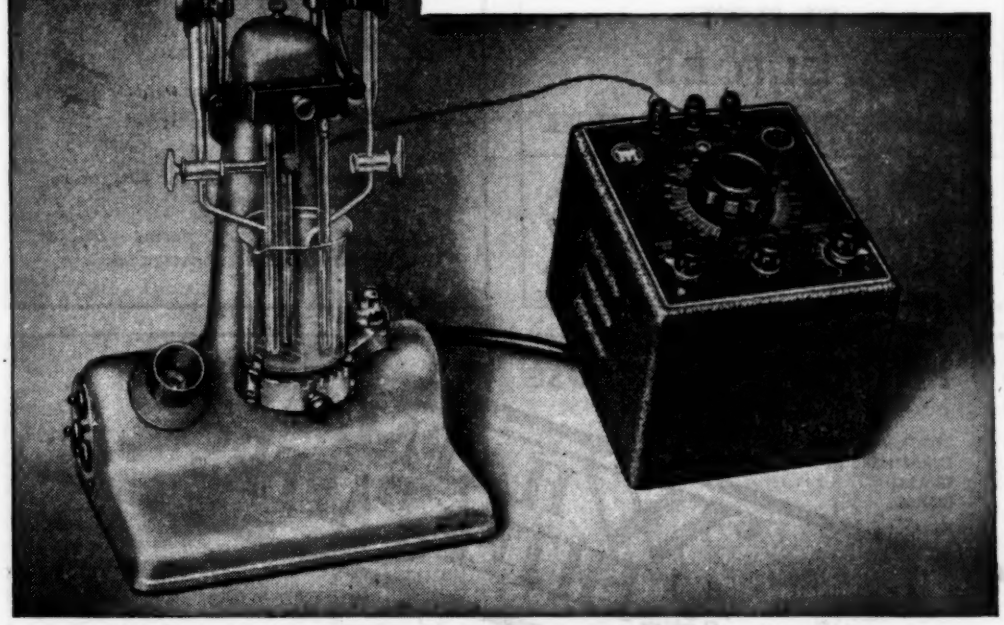

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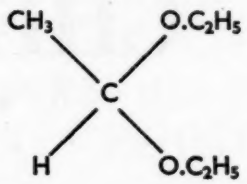

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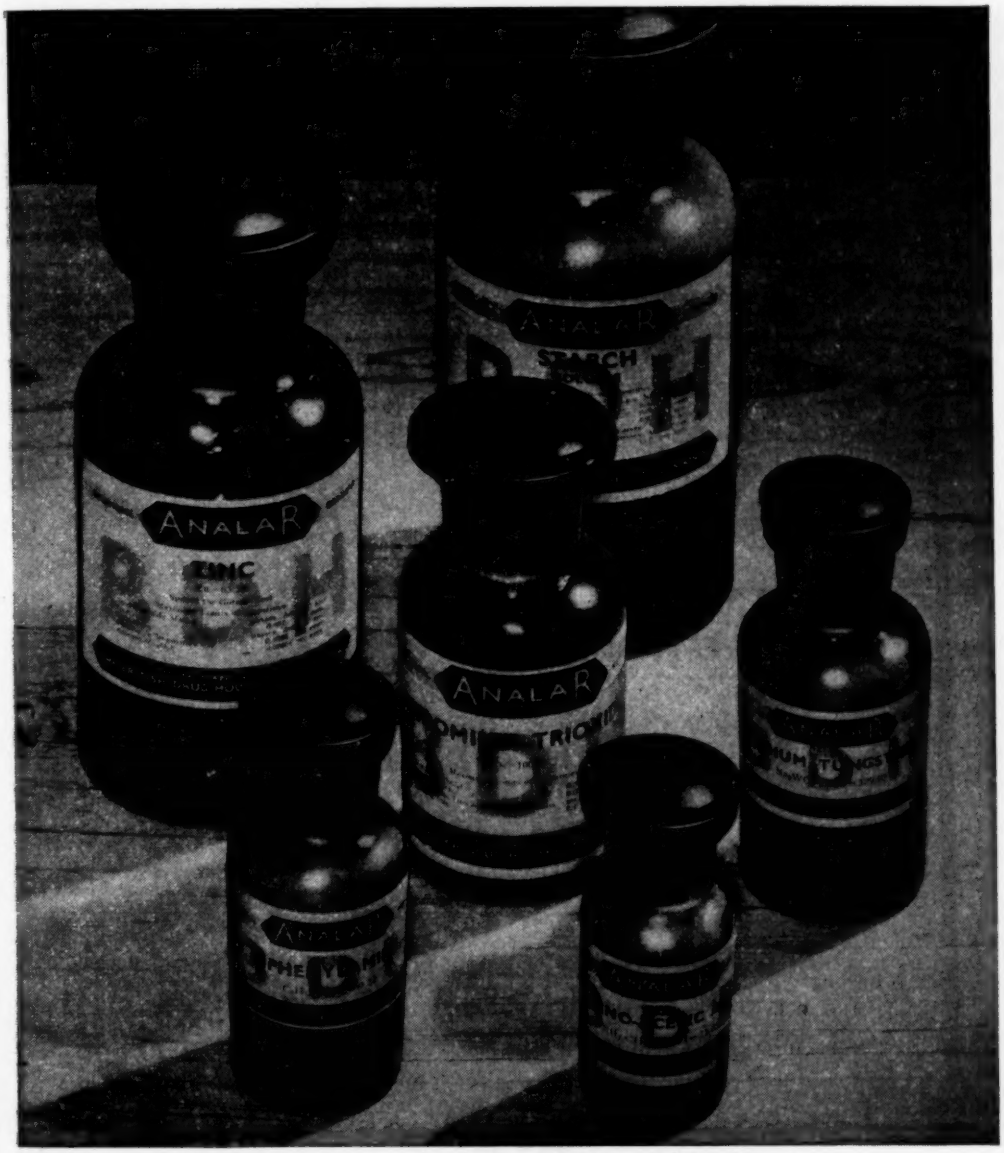

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which are geometrically irregular in this way would not be able to form crystalline arrangements. On the other hand, this type of irregularity cannot occur in the case of molecules bearing two identical atoms on the same chain carbon atom, and it is significant that such polymers (*e.g.*, polythene itself, polyvinylidene chloride, poly*iso*butene, the unsubstituted polyesters and polyamides) crystallise well. The point is of practical importance : anyone setting out to make new glass-like polymers would be ill-advised to use symmetrical monomers.

Discussion.

Dr. D. J. Crisp : The idea put forward by Mr. Bunn, that randomly arranged optical antipodes might account for the lack of crystallinity in certain vinyl polymers such as polyvinyl acetate, was suggested by Staudinger ("Die hochmolekularen organischen Verbindungen," Berlin, 1932, p. 114), and criticised by Meyer ("Natural and Synthetic High Polymers," New York, 1942, p. 106). The difficulty lies in the fact that polyvinyl alcohol, derived by simple hydrolysis of the acetate, presumably without intramolecular rearrangement, is crystalline. Hence structural regularity about the main valency chain does not appear to be the only factor.

Mr. C. W. Bunn : The apparent geometrical regularity of polyvinyl alcohol (the evidence for which is the crystalline *X*-ray diagram) does not prove that polyvinyl acetate is geometrically regular. If, in the hydrolysis, the acetate groups come off whole (*i.e.*, the break is between the oxygen and the chain carbon atom), then momentarily the chain carbon atom has a free bond, the hydrogen atom on this carbon atom might change over from one stereo-position to the other. In this case there is the possibility that geometrically regular polyvinyl alcohol might be produced from irregular polyvinyl acetate. Thus it is not certain that polyvinyl acetate has a regular structure.

Prof. Melville : If polyvinyl alcohol is reconverted into polyvinyl acetate, the latter is found to be again non-crystalline.

Mr. C. W. Bunn : That seems a more serious objection : from regular polyvinyl alcohol one would expect to get regular polyvinyl acetate, but even this is not certain ; a change of configuration may take place when there are free bonds on the chain carbon atoms, if the break occurs between the oxygen and the chain carbon atom. But whatever is the truth about this particular case, the statement I made is generally true—that those polymers whose molecules may be geometrically irregular through the occurrence of left- and right-handed groups indiscriminately along the chain are either non-crystalline (polystyrene, polymethyl methacrylate) or poorly crystalline (polyvinyl chloride, polyacrylonitrile), whilst those polymers in which such irregularity cannot occur (polythene, polyvinylidene chloride, poly*iso*butene) crystallise well. I do not think polyvinyl acetate has a regular structure and even if the explanation I have suggested of the polyvinyl alcohol–acetate case is not correct, then I think some other explanation will be found which is consistent with geometrical irregularity in the acetate.

Dr. Ian MacArthur : Structural discussion today has centred on the chain type of macromolecule. The characterising features of all types are the relative strength and stability of the constituent (as against the inter-) links. The nature of these, and particularly their directional bias, determine the conditions under which the metrical techniques are most serviceable. Where the polar groups are not too numerous, bulky, or reactive, and the physical state allows mobility, statistical and thermodynamic methods, as Dr. Gee has stressed, give a close approximation to experiment; entropies, not energies, are the dominant factor in long chains as such : chemical nature is subsidiary. The infra-red technique is more specific. With the speed and accuracy of the newer instruments, the present stage of collection, correlation, and semi-empirical diagnosis is still more profitable than approximate synthetic calculation.

I agree with most of Mr. Bunn's remarks, and appreciate that he deliberately restricted to crystallographic aspects. The view (Fankuchen, *Ann. Rev. Biochem.*, 1945, **14**, 210) that a complete crystallographic cell parameter determination is the sole or sometimes even the highest aim of an *X*-ray investigation in the macromolecular field, is unduly narrow. Macromolecules are usually protean systems with configuration a function of state of aggregation. In polythene, the confirmation, in the crystalline chain parts, of Müller's earlier structure for n-$C_{29}H_{60}$, is not more fundamental than the anomalies found in the determination, the composite crystalline–amorphous nature of the material, and the whereabouts of the small percentage of methyl groups; while structural progress in proteins has derived more real impetus and secured broader findings from the combined experimental fibrous protein and virus researches, synthetic model building, and co-operation with practical fibre industries, than from the purely

X-ray crystallographic approach. Precise atomic placings are excellent, but as a stage in indicating bond types, the genesis of aggregation, and the equilibria resulting from potential fields. Such features are often best investigated by selection and systematic treatment of the macromolecule, and by the co-operative use of all the relevant physicochemical methods. Among these the wave range of *X*-rays is specially serviceable to the physical chemist; but it is a tool to employ, not a subject for votaries; it gives evidence, not verdicts.

Quite apart from the fact that the full impact of *X*-rays on real matter is only now beginning to receive comprehensive notice, and that much of the information so yielded—questions of texture and secondary structure, deformation, thermal and elastic vibration systems, particle (as opposed to crystallite) size and orientation, degree of crystallinity, nature and degree of disorders—is frequently of more relevance than intracrystallite atomic arrangements, a too rigorous parameter analysis in macromolecules keeps length as a difficulty rather than as an opportunity. The advantages of small polar molecules to the *X*-ray analyst are that in packing neatly, they crystallise easily, have few parameters, and the answer is usually more or less known. The disadvantages are that bond lengths deduced are specially subject to local perturbation whose precise evaluation by quantum-mechanical calculation is in its earlier stages. When atomic parameters become too numerous for rigorous treatment, simply put in more! The asymptotic approach so made gives a more standard environment, proportionately diminishes end-group effects, and reduces many problems to two-dimensional ones, for the natural tendency of chains in aggregating to a minumum potential is to form a rod-like shape and pack in pseudo-hexagonal parallel array. Such packings are a function of molecular shape, polarity, and internal rigidity. To a first approximation they yield cells of standard cross-section and length corresponding to the unit involved. To a second approximation these dimensions do vary, and "straight" crystal analysis, on one individual only, fails to reveal them.

Long *n*-aliphatic chains form the simplest illustration. Long-chain *n*-paraffins usually build crystal cells with a standard cross-section and a length (C) given by $C/2 = k(n - 1) + p$, where n = carbon-atom content in chain, and k and p are constants. As n or temperature varies, polymorphic transitions appear, pseudo-rhombic giving place to pseudo-hexagonal or pseudo-monoclinic forms, but zigzag chain shape and packings are essentially the same. With the insertion of small polar groups rigidly attached to the chain axis (*e.g.*, in *n*-ketones) polymorphism disappears, the addition of dipole layer to van der Waals chain forces having a stabilising effect, especially with respect to temperature variation. The position of the C=O substituent along the chain causes systematic variation. The degree of stability increases with the dipole moment of the group inserted. In all cases, temperature increase causes a nearer approach to a radial symmetry which may (certain paraffins and alcohols) or may not (acids) be reached before melting. The phenomenon argues an increased rotational or torsional vibration about the chain axis, probably of a co-operative type. The nature of this is helpfully investigated through thermal energies (Garner), intensity analysis along the chain (MacArthur), or by temperature–polarisation studies on *cis*- or *trans*-diketones (Müller). Transitional energies can be subdivided into chain and end-group elements. In general, strain in bond lengths and angles may be indicated by abnormal heats of combustion (poly*iso*butylene; Polanyi), or its absence reduces isomeric possibilities for test (benzene hexachlorides). Localised molecular weighting is valuable. Swelling or isotopic replacements may indicate particular (*e.g.*, hydrogen-bond) links. Force field theory is useful in simple cases. Although the plate (graphite, clays) and skeleton (protein) types are a natural extension from chains, they lie outside present discussion; but, particularly here, the new technique of the electron microscope with its resolving power of 25 A. has, in conjunction with *X*-rays, been of valuable and potentially enormous service.

It may well be, therefore, that the fundamental structural developments in macromolecules will be achieved, not through routine precision crystal analysis, but, as instanced in the pioneer long-chain work of the Royal Institution and the Bristol school, and in the fibre methods at Leeds, in co-ordination with ancillary techniques. Scientifically, this demands an extensive physicochemical background; technically, greater concentration on *X*-ray power, sensitivity and speed of recording, and flexibility in conditioning specimens while undergoing *X*-radiation.

58. *Respiratory Stimulants. Part I. Fully-substituted Ureas derived from αω-Alkylenediamines.*

By W. R. Boon.

Reaction of an *NN'*-disubstituted ethylene- or trimethylene-diamine with carbonyl chloride gives a mixture of the cyclic urea and the biscarbamyl chloride. The cyclic ureas show some activity as respiratory stimulants. The bis-ureas, X·CO·NR·[CH_2]$_n$·NR'·CO·Y (when X and Y are secondary amine residues), obtained by reaction of the biscarbamyl chlorides with secondary amines, or preferably of a diamine with a carbamyl chloride, are in general even more potent substances. The synthesis of compounds in which R and R' are straight or branched hydrocarbon chains or are substituted by ether groups is described. Examples are given of the use of dialkylamines, cyclic bases, and dialkylamines containing ether linkages. The relationship between constitution and activity is briefly discussed.

Since Uhlmann (*Z. ges. exp. Med.*, 1924, **43**, 566) introduced pyridine-3-carboxydiethylamide (" Nikethamide ", B.P.) into medicine as a cardiac stimulant and analeptic, this substance has been widely used to combat respiratory and circulatory collapse associated with surgical emergencies. Although no conclusive evidence has ever been offered for any direct action of this substance on the heart, it is recognised that it is a powerful stimulant of the respiration, particularly if this function has been depressed by previous administration of narcotics such as morphine or the barbiturates. Nikethamide, and the other substances commonly used as analeptics, suffer from the disadvantage that the dose stimulating the respiration is very close to that causing convulsions. In addition, Das (*Quart. J. Exp. Physiol.*, 1939, **29**, 355) has shown that in cases of severe respiratory depression produced by hexobarbitone the administration of nikethamide frequently fails to stimulate the respiration and may even augment the initial depression.

There have been many attempts to obtain better respiratory stimulants among the general class of acid amides. In the pyridine series the following may be mentioned: diethylamides of pyridine-2- and -4-carboxylic acid and of 2 : 2 : 5 : 5-tetramethylpyrroline-3-carboxylic acid (Gryszkiewicz-Trochimowski, *Rocz. Chem.*, 1931, **11**, 193); pyridine-2 : 5-biscarboxydiethylamide and some complex amides of nicotinic acid (*idem*, *ibid.*, 1934, **14**, 335). Graf, Theyerl, and Purkert (*J. pr. Chem.*, 1933, **138**, 259) prepared the diethylamides of a number of nuclear-substituted nicotinic acids including pyridine-3 : 5-dicarboxylic acid; similarly F.P. 798,639 (S. C. I. Basle) claims the preparation of amides of pyridine-*o*-dicarboxylic acids as respiratory stimulants. A closely related group of substances, pyridine-3-carboxyurethanes, is described in D.R.-P. 603,733 (S. C. I. Basle).

Among other heterocyclic systems, amides (usually the diethylamides) of the following acids or groups of acids have been reported as possessing respiratory stimulant activity: pyrazinecarboxylic acid (Merck, E.P. 451,304); *iso*oxazole-, thiazole-, and pyrazole-carboxylic acids (Heffer and Reinert, *Arch. int. Pharm. Ther.*, 1937, **56**, 211; Hoffman–La Roche, E.P. 451,913); tetrazole-5-carboxylic acid (Gryszkiewicz-Trochimowski, *Rocz. Chem.*, 1933, **138**, 259); glyoxaline-4(5)-carboxylic acid (Weidenhagen and Wegner, *Ber.*, 1937, **70**, 2309); indole-3-carboxylic acid, indole-3-acetic acid, octahydroindole-3-acetic acid and thionaphthen-3-carboxylic acid; various thiazole-carboxylic acids (Erlenmeyer and von Meyenburg, *Helv. Chim. Acta*, 1937, **20**, 204; Boon, *J.*, 1945, 601) and 1 : 2-pyrone-5-carboxylic acid (J. R. Geigy A.G., E.P. 537,670).

Among carbocyclic compounds may be mentioned phthalic acid bisdiethylamide—the corresponding derivatives of *iso*- and tere-phthalic acid are said to be considerably less active (Landshoff and Meyer, E.P. 443,396)—and the dimethyl- or diethyl-amides of di- or tri-methoxy- or -ethoxy-benzoic acids (Hoffman–La Roche, E.P. 403,892).

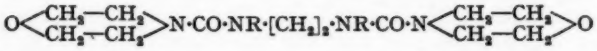
Although in most of the above publications there are statements that some or all of the products described show respiratory stimulant activity, there is a noteworthy absence of any detailed pharmacological report in nearly all cases. Only two of the many compounds described appeared to have attained to clinical use: phthalic acid bisdiethylamide has been used, mainly in Germany, under the name " Neospiran ", and 3 : 5-dimethyl*iso*oxazole-4-carboxylic acid diethylamide is used under the name " Cycliton ".

A paper by Aeschlimann (*Festschr. E. C. Barrell*, Basle, 1936, 246; *Chem. Zentr.*, 1936, III, 2944) suggested the initial experiments in the present work. In this paper it was shown that, *inter alia*, tetraethylurea and piperazine-1 : 4-biscarboxydiethylamide possessed respiratory stimulant properties. It was decided, therefore, to examine the reaction between carbonyl

chloride and some *NN'*-dialkyl-ethylene- or -trimethylene-diamines which was expected to give either a 1 : 3-dialkyliminazolidine-2-one (or the corresponding hexahydropyrimidone) or a biscarbamyl chloride. Both of these types of compound were considered to be of interest. The former may be regarded as a fully alkylated urea, and the latter as a derivative of piperazine-1 : 4-dicarboxylic acid in which one side of the ring has been broken. Both the cyclic ureas and the bisureas resulting from the reaction of the biscarbamyl chlorides with secondary amines showed respiratory stimulant activity. In general, the latter class of compound was more active; this fact, combined with the greater possibilities of chemical elaboration offered by it, led to its selection for more detailed study.

Although a detailed report on the pharmacology of these compounds will be published elsewhere, the following notes on the main conclusions to be drawn from results of their pharmacological evaluation by Dr. J. Raventos are given so that the lines of development of the chemical work may be more readily appreciated.

In the series of compounds represented by the general formula $X{\cdot}CO{\cdot}NR{\cdot}[CH_2]_n{\cdot}NR'{\cdot}CO{\cdot}Y$, lengthening the hydrocarbon chain between the diamine nitrogen atoms increases the activity if X, Y, R, and R' are kept constant, but at the same time the solubility in water is decreased and the toxicity is raised. The nature of the groups R and R' has a very pronounced effect on the activity; in general, a regular increase occurs from methyl to *n*-butyl, and branching of the chain, unsaturation, or the introduction of ether linkages reduces the activity. In the series of compounds



activity increases in the order

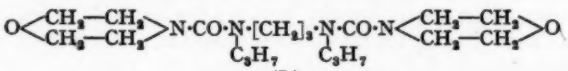
$$R = Me = CMe_3 = CHMeEt < Et < CHMe_2 < CH_2{\cdot}CH{:}CH_2 < CH_2{\cdot}CHMe_2 < n\text{-}Pr < n\text{-}Bu$$

In symmetrical compounds where X = Y the degree of activity is generally in the following order :

$$NMe{\cdot}C_2H_4{\cdot}OMe < NMe_2 < O\langle \begin{matrix} CH_2{-}CH_2 \\ CN_2{-}CN_2 \end{matrix} \rangle N < NMe{\cdot}C_2H_4{\cdot}OEt < NEt{\cdot}C_2H_4{\cdot}OMe < NEt{\cdot}C_2H_4{\cdot}OEt < NMe{\cdot}CHMe_2 < NEt_2 < NC_5H_{10}$$

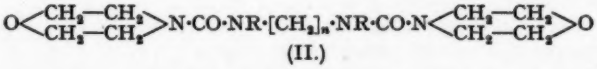
Unsymmetrical compounds, in general, possess the mean of the activities of the two related symmetrical compounds.

Although these conclusions are true in outline, there are numerous exceptions; thus NN'-*di*-n-*propyltrimethylenediamine*-NN'-*biscarboxymorpholide* (I) possesses only one-twelfth of the activity of the corresponding ethylenediamine derivative.



(I.)

In spite of the above generalisations of the effect of changes in portions of the structure on the activity of the product, it is, nevertheless, true that the value of a compound depends more on a suitable balancing of different groups within the molecule. In general, it appears that the most active compounds are those which are distributed approximately equally between water and hydrocarbon solvents; this is most readily illustrated by the compounds of general formula (II).



(II.)

If the strongly hydrophilic morpholine residue is combined with a short-chain substituent, R = Me or Et, the products have very high water-solubility with low solubility in hydrocarbon solvents and low respiratory-stimulant activity. As R is increased to propyl or *n*-butyl the solubility in hydrocarbon solvents increases and very potent stimulants are obtained, with approximately twelve times the activity of nikethamide. Both of these substances have a prolonged period of action, longer than that of picrotoxin, which itself is some ten times longer than that of nikethamide. Unlike picrotoxin, however, these two substances stimulate the depressed respiration at doses far removed from those causing convulsions or death. Prolonged activity appears to be associated with a combination of the morpholine residue with a three- or four-carbon substituent on the diamine nitrogen. Replacing the morpholine residue by another hydrophilic grouping such as methyl-2-ethoxyethylamine, or lengthening the diamine

chain in conjunction with a morpholine residue associated with a methyl or ethyl group on the diamine nitrogen atoms, does not lead to prolonged action.

The two most interesting compounds with a short duration of action are NN′-*dimethyltrimethylenediamine*-NN′-*biscarboxydiethylamide* and NN′-*di*-n-*propylethylenediamine*-NN′-*biscarboxydimethylamide*. Both of these substances are approximately twice as active as nikethamide, but whereas the ratio of convulsant dose to stimulant dose is 7·5 in the case of the former compound compared with 2·8 for nikethamide, the latter compound is devoid of convulsant action. Both of these substances, unlike nikethamide, may be administered repeatedly without any habituation. By the continuous administration of a suitable mixture of a short-acting barbituric acid derivative, such as hexobarbitone, and either of these compounds it is possible to maintain an animal under anæsthesia with its respiratory activity at the normal conscious level.

Derivatives of ethylene- and trimethylene-diamine, reacting with carbonyl chloride, gave approximately equal yields of urea and carbamyl chloride.

Conversion of the biscarbamyl chlorides into bisureas by reaction with secondary amines proceeded smoothly in all cases; this reaction in fact was used to identify the biscarbamyl chlorides, since in most cases it was not possible to purify these substances for analysis as they were liquids which decomposed on distillation with loss of carbonyl chloride and formation of what appeared to be linear polyureas which could not be purified. In general, it was more convenient to prepare the bisurea by reaction of the diamine with a carbamyl chloride. In most cases the reaction proceeded substantially to completion, but in others appreciable quantities of amino-ureas were obtained. In general, the reactivity of the carbamyl chloride (Z·COCl) appeared to be in the following order :

$$Z = NMe_2 > NEt_2 > NC_5H_{10} > O\langle\begin{matrix}CH_2—CH_2\\CH_2—CH_2\end{matrix}\rangle N > NEt\cdot C_2H_4\cdot OEt > N(C_2H_4\cdot OEt)_2$$

The nature of the substituent on the diamine nitrogen atom also affected the result; alkoxyethyl groups, in particular, produced a marked decrease in reactivity.

Unsymmetrical bisureas of type X·CO·NR·$[CH_2]_n$·NR·CO·Y were made by reaction of a carbamyl chloride with an excess of diamine to give a monourea of type X·CO·NR·$[CH_2]_n$·NRH, which was then caused to react with a different carbamyl chloride.

Unsymmetrical bisureas of the type X·CO·NR·$[CH_2]_n$·NR′·COX were readily made by reaction of the appropriate unsymmetrical diamine with a carbamyl chloride.

The numerous diamines required in this work have been prepared by three methods, the choice of method being governed partly by convenience and partly by the unsuitability of the alternative routes in a particular case.

The most convenient method for preparing *NN′*-dimethylethylenediamine, the simplest member of the series, was by decomposition of *NN′*-di-(4-nitrosophenyl)-*NN′*-dimethylethylenediamine with sodium hydrogen sulphite, essentially according to the method of Esch and Marckwald (*Ber.*, 1900, **33**, 762). The parent *NN′*-diphenyl-*NN′*-dimethylethylenediamine was best prepared by a modification of the method of Dunlop and Jones (*J.*, 1909, **95**, 417), involving condensation of ethylene dibromide with methylaniline; the alternative method of Thorpe and Wood (*J.*, 1913, **103**, 1608), involving condensation of ethylene dibromide with dimethylaniline, consistently failed, 1 : 4-diphenylpiperazine being the only product identified. Condensation of ethylene dibromide with *iso*propylaniline did not proceed so readily, and some 1 : 4-diphenylpiperazine was formed as well as NN′-*diphenyl*-NN′-*diiso*-*propylethylenediamine*; none of the former was detected when ethylene dibromide was condensed with methyl- or ethyl-aniline. The diamine derivative could not be converted into *NN′*-di*iso*propylethylenediamine.

An attempt was made to prepare *NN′*-diphenyl-*NN′*-diethyltetramethylenediamine by reaction of ethyl-2-chloroethylaniline with sodium. Although the product analysed satisfactorily for nitrogen it did not give *NN′*-diethyltetramethylenediamine on nitrosation and subsequent hydrolysis.

All of the above compounds have been converted into the corresponding disecondary amines by the action of sodium hydrogen sulphite on their nitroso-derivatives (cf. Esch and Merckwald, *loc. cit.*). None of the nitroso-compounds has been isolated in the pure state : this was usually difficult and was not necessary. Where a hydrochloride of the nitroso-compound separated, this was filtered off and decomposed by heating with sodium hydrogen sulphite solution; otherwise an excess of the latter reagent was added to the reaction mixture resulting from the nitrosation. Yields were variable, but owing to the nature of the reactions involved it is not

possible to decide the relative efficiency of the operation at different stages in any particular case.

Many disecondary diamines have been made by hydrolysis of the corresponding *p*-toluenesulphonamide derivatives with 80% sulphuric acid at 140° instead of the less convenient method (Schneider, *Ber.*, 1895, **28**, 3074) involving heating with fuming hydrochloric acid under pressure. This method failed with *di*-p-*toluenesulphonyl*-NN′-*diallylethylenediamine* which charred when it was mixed with the acid, and with *di*-p-*toluenesulphonyl*-NN′-*di*iso*propylethylenediamine*.

The requisite sulphonamides were made either by alkylating the toluenesulphonyl derivative of the primary diamine or by reaction between a sulphonamide of a primary monoamine and a suitable dihalogeno-compound. The corresponding reaction between *p*-toluenesulphonamide and a dihalogeno-compound occurs satisfactorily only with ethylene dibromide. With higher alkylene dibromides the complications resulting from ring formation render the method unworkable. For instance, from the condensation of trimethylene dibromide with *p*-toluenesulphonamide it was possible to isolate di-*p*-toluenesulphonyltrimethylenediamine in only very poor yield; *p*-toluenesulphonyltrimethyleneimine and 1 : 5-di-*p*-toluenesulphonylbistrimethylenediamine were also identified. Marckwald and v. Droste-Huelshoff (*Ber.*, 1898, **31**, 3265) identified only the last two products from a similar reaction. Usually the sulphonamide of the primary diamine was alkylated in aqueous alcoholic solution.

The condensation of the dihalogeno-compounds with the sodium salts of *p*-toluenesulphonalkylamides was carried out in boiling xylene. No reaction occurred between ethylene dibromide and *p*-toluenesulphon*iso*butylamide under these conditions; this is in agreement with Wedekind's observation (*Ber.*, 1909, **42**, 3941) that the unstable sodium salt of *p*-toluenesulphon*iso*butylamide is very unreactive.

The direct formation of a disecondary amine by reaction of a dihalide with an excess of a primary amine has been used in several cases, mainly those in which one or other of the above methods broke down, *e.g.*, in the preparation of NN′-*diallyl*- and NN′-*di*iso*propyl-ethylenediamine*, or were markedly inefficient, *e.g.*, NN′-*di*iso*butylethylenediamine*, or were judged to be inapplicable, *e.g.*, NN′-*di*-tert.-*butylethylenediamine* or NN′-*di*-(2-*ethoxyethyl*)*ethylenediamine*.

Dihalogeno-compounds in which the halogen atoms are separated by more than two carbon atoms usually give very poor results. In general, where free choice is possible, methods involving the degradation of a suitable tertiary or quaternary nitrogen compound are better than the direct synthesis of a disecondary amine by this last method.

The 2-alkoxyethylamines were readily obtained by catalytic reduction of the corresponding alkoxyacetonitriles in presence of Raney nickel. This method of preparation is much simpler than those reported in the literature.

A series of alkyl-alkoxyethylamines as well as *di*-(2-*ethoxyethyl*)*amine* have been prepared from the corresponding aniline derivatives by hydrolysis of the nitroso-compounds. An alternative procedure used in some cases was alkylation of an alkoxyethylamine: this is more convenient if the alkoxyethylamines are available.

Experimental.

Preparations marked by an asterisk were made by Dr. J. A. Hendry. Microanalyses are by Mr. E. S. Morton M. p.'s are corrected.

(1) *Aniline Derivatives.*—*NN′*-Diphenyl-*NN′*-dimethylethylenediamine was made by the following modification of Dunlop and Jones's method (*loc. cit.*). Ethylene dibromide (1128 g., 6 mols.), methylaniline (1819 g., 17 mols.), and anhydrous sodium carbonate were heated under reflux with stirring at 105° for 24 hours. The excess of methylaniline was then removed by steam-distillation, and the residue was cooled while stirring was continued, and filtered off. The product was washed thoroughly with cold water and air-dried; yield 1355 g. (83%), m. p. 49°, raised by crystallisation from methanol to 50°. The crude product was suitable for conversion into *NN′*-dimethylethylenediamine. The following amines were made by similar methods: *NN′*-diphenyl-*NN′*-diethylethylenediamine, m. p. 75°, yield 90%; *NN′*-diphenyl-*NN′*-dimethyltrimethylenediamine, b. p. 230°/16 mm., m. p. 46°, yield 84%; *NN′*-diphenyl-*NN′*-diethyltrimethylenediamine, b. p. 236°/20 mm., m. p. 39° (from petrol, b. p. 60—80°); yield 85%; Fröhlich (*Ber.*, 1907, **40**, 764) describes this compound as an uncrystallisable oil.

NN′-*Diphenyl*-NN′-*di*iso*propylethylenediamine.* The crude *product*, b. p. 234—239°/28 mm., contained much 1 : 4-diphenylpiperazine which was separated by crystallisation from ethanol; the residue from the evaporation of the mother-liquors was recrystallised from petrol (b. p. 60—80°); m. p. 62°, yield 21% (Found: C, 81·0; H, 9·05; N, 9·6. $C_{20}H_{28}N_2$ requires C, 81·0; H, 9·45; N, 9·45%). By heating at 120° for 17 hours under an air condenser the yield was raised to 60% with only a trace of piperazine formation.

Ethyl-2-chloroethylaniline was made by the following modification of the method given in D.R.-P. 650,259 (I.G. Farbenind. A.G.; Friedländer, Vol. 22, p. 286): To thionyl chloride (190 g., 1·6 mols.), dissolved in toluene (100 c.c.), was added with stirring below 2° a solution of ethyl-2-hydroxyethylaniline (247 g., 1·5 mols.) in toluene (650 c.c.). After being stirred at room temperature overnight, the

reaction mixture was poured on ice, basified with sodium carbonate, and the toluene layer separated. Distillation of the toluene solution after drying (Na_2SO_4) gave 235 g. (82·5%) of ethyl-2-chloroethylaniline, b. p. 163—164°/42 mm. *Ethyl-3-chloropropylaniline* was made in a similar manner from ethyl-3-hydroxypropylaniline in 64% yield; b. p. 161°/30 mm. (Found: N, 7·4. $C_{11}H_{16}NCl$ requires N, 7·1%). The *hydroxy*-compound (b. p. 168—172°/16 mm.) was made by condensation of trimethylene chlorohydrin (Gough and King, *J.*, 1928, 2439) with ethylaniline substantially according to Laun's method (*Ber.*, 1884, **17**, 677) for the preparation of ethyl-2-hydroxyethylaniline (Found: C, 73·6; H, 9·3; N, 8·0. $C_{11}H_{17}ON$ requires C, 73·7; H, 9·5; N, 7·8%).

NN'-*Diphenyl*-N-*methyl*-N'-*ethylenediamine*. Methylaniline (870 g., 8·1 mols.) and ethyl-2-chloroethylaniline (393 g., 2·15 mols.) were heated together on the steam-bath for 16 hours. Water (500 c.c.) and 32% sodium hydroxide (175 c.c.) were then added, and the oily layer separated and distilled. The product had b. p. 226—228°/16 mm., m. p. after recrystallisation from methanol 35°; yield 450 g. (83%). NN'-*Diphenyl*-N-*methyl*-N'-*ethyltrimethylenediamine* was similarly obtained in 84% yield from methylaniline and ethyl-3-chloropropylaniline; it had b. p. 216°/16 mm. (Found: N, 10·7. $C_{18}H_{24}N_2$ requires N, 10·45%).

Ethyl-2-methoxy- and -2-ethoxy-ethylaniline were first made by condensation of the appropriate glycol ether *p*-toluenesulphonate with ethylaniline (B.P. 422,843). The following method was more convenient: Ethyl-2-hydroxyethylaniline (375 g., 2·25 mols.) was dissolved in toluene (750 c.c.) and the solution dried by distillation until a clear distillate was obtained; after it had cooled to 40°, sodium (46 g., 2 mols.) was added. When the initial reaction had subsided, the mixture was boiled for 6 hours to dissolve all the sodium. The solution of the sodium derivative was cooled to 10°, and methyl sulphate (252 g., 2 mols.) was added with stirring below 25°. After standing for 48 hours, the solution was washed with water and extracted with dilute hydrochloric acid. The oil which separated on basifying the acid solution was distilled, giving 325 g. (80%) of ethyl-2-methoxyethylaniline, b. p. 130°/11 mm.

Methyl-2-methoxyethylaniline, b. p. 125°/15 mm., and *methyl-2-ethoxyethylaniline*, b. p. 142°/23 mm. (Found: C, 73·4; H, 9·5. $C_{11}H_{17}ON$ requires C, 73·6; H, 9·0%), were made similarly.

*Di-(2-ethoxyethyl)aniline.** Di-(2-hydroxyethyl)aniline (271 g., 1·5 mols.), dissolved in toluene (500 c.c.), was added with stirring during 45 minutes to a suspension of sodium (69 g., 3 mols.) in toluene (150 c.c.) the temperature being kept at 100—110°. After a further 6 hours' heating, the temperature was lowered to 20°, and methyl sulphate (462 g., 3·66 mols.) in toluene (500 c.c.) was added so that the temperature did not rise above 30°. After 12 hours' stirring at room temperature, water (500 c.c.) was added, and the toluene layer separated and extracted with dilute hydrochloric acid. The extract was basified with sodium hydroxide, extracted with benzene, and the extract dried (Na_2SO_4). Distillation gave 140 g. (39%) of *di-(2-ethoxyethyl)aniline*, b. p. 187—189°/25 mm. (Found: C, 70·65; H, 9·45; N, 6·1. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7; N, 5·9%).

(2) *Sulphonamides.—Condensation of* p-*toluenesulphonamide and trimethylenedibromide.* *p*-Toluenesulphonamide (213 g., 1·25 mols.) was dissolved in ethanol (325 c.c.) and 32% sodium hydroxide (153 g., 1·25 mols.); trimethylene dibromide (126 g., 0·625 mol.) was added, and the whole heated under reflux for 15 hours. The alcohol was distilled off, and water added together with sufficient hydrochloric acid to make the residue acid to Congo-red. The supernatant liquid was poured off, and the residual oil triturated with an excess of 15% sodium hydroxide. The solid which separated was filtered off and fractionally crystallised from ethanol to give *p*-toluenesulphontrimethyleneimide, m. p. 120°, and 1 : 5-di-*p*-toluenesulphonylbistrimethylenediamine, m. p. 215°. By acidification of the alkaline solution, crude di-*p*-toluenesulphonyltrimethylenediamine was obtained contaminated with much *p*-toluenesulphonamide. The latter was removed by repeated boiling out with water, and the trimethylenediamine derivative purified by three crystallisations from ethanol; yield 35 g., m. p. 148°.

Di-*p*-toluenesulphonylhexamethylenediamine was made in practically theoretical yield from hexamethylenediamine and *p*-toluenesulphonyl chloride by the normal Schotten–Baumann procedure; m. p. 149° (from ethanol) (Found: C, 56·1; H, 7·1; N, 6·9. Calc. for $C_{20}H_{28}O_4N_2S_2$: C, 56·6; H, 6·7; N, 6·7%).

Di-p-*toluenesulphonyldialkyl-alkylenediamines.* (A) To the di-*p*-toluenesulphonylalkylenediamine (1 mol.), dissolved in methanol and 32% sodium hydroxide (1·1 mols.) cooled in an ice-bath, the appropriate alkyl sulphate or alkyl halide (2·25 mols.) was added during 2 hours, and after a further hour's stirring at room temperature, reaction was completed by 4 hours' heating under reflux. After cooling, the product was filtered off, washed with a little methanol, then with water and dried.

(B) To sodium (2 mols.) suspended in xylene at 105°, ethanol (3·2 mols.) was added with stirring. After cooling to 60°, the *p*-toluenesulphonalkylamide (2 mols.) was added, and the ethanol removed by distillation. The alkylene dibromide (1 mol.) was then added, and heating continued at 130—135° for 17 hours. The reaction mixture was then cooled to 20°, and the solid filtered off and washed first with methanol and then with water. Table I gives details of the compounds prepared. p-*Toluenesulphonmethylisopropylamide*, required for the preparation of methyl*iso*propylamine, was made in 89% yield by method B from *p*-toluenesulphon*iso*propylamide and methyl sulphate; b. p. 226°/40 mm., m. p. 78° (from petrol, b. p. 60—80°) (Found: C, 58·7; H, 7·1; N, 6·2. $C_{11}H_{17}O_2N_S$ requires C, 58·2; H, 7·5; N, 6·2%).

(3) *Diamines.*—The following are details of typical experiments involving the three different methods employed.

(A) *By hydrolysis of a di-*p-*toluenesulphonyl derivative.* The di-*p*-toluenesulphonyl derivative (1 mol.) was dissolved with stirring in concentrated sulphuric acid (98%, 8·2 mols.), water (9 mols.) added, and the resulting suspension heated with stirring for 7 hours at 140—145°. It was then cooled, diluted with water, and made alkaline to Clayton-yellow by addition of 32% sodium hydroxide. This solution was then steam-distilled until the distillate was only faintly alkaline to brilliant-yellow. After the distillate had been acidified to Congo-red by hydrochloric acid, it was evaporated to dryness. The free base was obtained by dissolving the dihydrochloride in a 10% excess of 32% sodium hydroxide, and the solution evaporated to dryness under reduced pressure. The distillate was then saturated with sodium hydroxide, the oily layer separated, dried over potassium hydroxide, and finally distilled from sodium.

TABLE I.

Di-p-toluenesulphonamides, $C_7H_7 \cdot SO_2 \cdot NR \cdot [CH_2]_n \cdot NR \cdot SO_2 \cdot C_7H_7$.

R.	*n*.	Method of prep.	Yield, %.	M. p.	Solvent.	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me	2	A	85	164°	HOAc	$C_{18}H_{22}O_4N_2S_2$	54·4	6·7	7·3	54·5	6·1	7·1
Et	2	A	60	158	,,	$C_{20}H_{26}O_4N_2S_2$	56·35	6·5	6·7	56·5	6·6	6·6
Pr$^{\alpha}$	2	A	66	122	,,	$C_{22}H_{30}O_4N_2S_2$	58·8	7·4	6·2	58·3	7·2	6·2
Pr$^{\beta}$	2	A	8	221	$CH_2(OMe) \cdot CH_2 \cdot OH$	$C_{22}H_{30}O_4N_2S_2$	58·4	6·95	6·2	58·3	7·2	6·2
Allyl	2	A	75	146	HOAc	$C_{22}H_{26}O_4N_2S_2$	59·1	6·0	6·3	58·7	6·2	6·2
n-Bu	2	A	66	119	MeOH	$C_{24}H_{34}O_4N_2S_2$	59·5	7·3	5·9	59·9	7·5	5·8
iso-Bu	2	A	19	143	EtOH	$C_{24}H_{34}O_4N_2S_2$	60·1	7·9	5·5	59·9	7·5	5·8
Me	3	A	50	113	MeOH	$C_{19}H_{28}O_4N_2S_2$	56·0	6·4	6·95	55·6	6·34	6·8
Et	3	A	—	68	EtOH	$C_{21}H_{30}O_4N_2S_2$	—	—	6·2	—	—	6·4
Pr$^{\alpha}$	3	B	57	47 (b. p. 280—290°/0·1 mm.)	Petrol (b. p. 40—60°)	$C_{23}H_{34}O_4N_2S_2$	59·3	7·1	5·85	59·2	7·2	6·0
Me	4	B	88	131	EtOH	$C_{20}H_{28}O_4N_2S_2$	57·2	7·2	6·2	56·7	6·6	6·6
Me	5	B	98	61 (b. p. 285°/0·4 mm.)	,,	$C_{21}H_{30}O_4N_2S_2$	57·2	6·9	6·3	57·5	6·85	6·4
Me	6	A	84	140	HOAc	$C_{22}H_{32}O_4N_2S_2$	57·9	7·0	6·3	58·4	7·1	6·2
Et	6	A	81	115	EtOH	$C_{24}H_{36}O_4N_2S_2$	60·0	7·5	6·2	59·9	7·5	5·8

(B) *From a dianilino-derivative.* The *NN'*-diphenyl-*NN'*-dialkylalkylenediamine (1 mol.) was dissolved in concentrated hydrochloric acid (6·3 mols.) and diluted with ice (92·5 mols.). Sodium nitrite (2·22 mols.) in approximately twice its weight of water was then added with stirring during 30 minutes. After a further 30 minutes' stirring, the precipitated nitroso-compound was filtered off, pressed dry, suspended in a 20% aqueous solution of sodium hydrogen sulphite (7·5 mols.), and heated at 90—95° for 5 hours. The resulting solution was then made acid to Congo-red by addition of concentrated hydrochloric acid and concentrated to half its volume. This solution, after being made alkaline to Clayton-yellow by addition of solid sodium hydroxide, was steam-distilled, and the hydrochloride and base isolated as above.

In the preparation of *N*-methyl-*N'*-ethylethylenediamine, the hydrochloride of the nitroso-compound separated slowly and was filtered off after the reaction mixture had stood in ice for 17 hours.

(C) *By reaction of an alkylene dibromide with a primary amine.* The bromide (1 mol.), amine (5 mols.), and water (*ca.* 3 mols.) were heated under reflux for 15 hours. An excess of 32% sodium hydroxide was then added, and the excess of primary amine removed by distillation. The residual solution was then distilled to dryness under reduced pressure, and the diamine salted out from the distillate with solid sodium hydroxide, dried, and distilled in the usual way. The reaction with methyl- or *iso*propyl-amine was carried out in an autoclave. With allylamine or 2-methoxy- or 2-ethoxy-ethylamine the reaction in the early stages was vigorously exothermic. Details of the various preparations are given in Table II. None of the free bases was analysed owing to the marked tendency of most of them to take up water and carbon dioxide, but most of the *hydrochlorides* were analysed.

(4) *Carbamyl Chlorides from Secondary Amines.*—Dimethyl- and diethyl-carbamyl chlorides were prepared essentially according to the method of Lumière and Perrin (*Bull. Soc. chim.*, 1904, **31**, 689). Attention to the following points gave a consistently good yield (75%); the amine in toluene was added to an excess (*ca.* 3 mols.) of carbonyl chloride in toluene below — 10°; the amine hydrochloride was best removed by washing with ice-water followed by rapid drying of the toluene solution with calcium chloride. The following were also prepared by this method: Piperidine-*N*-carboxychloride, b. p. 119°/18 mm.; *morpholine-N-carboxychloride*, b. p. 137—138°/33 mm. (Found: C, 40·05; H, 5·5; N, 9·1. $C_5H_8O_2NCl$ requires C, 40·2; H, 5·35; N, 9·3%); *di-(2-ethoxyethyl)carbamyl chloride*,* b. p. 165°/19 mm. (Found: C, 48·15; H, 8·4; N, 6·4. $C_9H_{18}O_3NCl$ requires C, 48·3; H, 8·05; N, 6·3%); and *ethyl-2-ethoxyethylcarbamyl chloride*,* b. p. 108°/20 mm. (Found: C, 47·1; H, 7·85; N, 7·5. $C_7H_{14}O_2NCl$ requires C, 46·8; H, 7·8; N, 7·8%).

(5) 2-*Alkoxyethylamines.*—These were made by reducing the following alkoxyacetonitriles over a Raney nickel catalyst; yields varied from 65 to 75%: methoxyacetonitrile (Henze and Righer, *J. Amer. Chem. Soc.*, 1934, **56**, 1350), ethoxyacetonitrile (Gautier, *Ann. Chim.*, 1909, **16**, 302), *iso*propoxyacetonitrile (Henze *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 1222), and *n*-butoxyacetonitrile (Hurd and Fowler, *ibid.*, 1939, **61**, 252). The following two amines are new. 2-*iso*Propoxyethylamine, b. p. 116—118°; *picrolonate*, from ethanol, m. p. 201—202° (Found: C, 48·6; H, 5·75; N, 19·1. $C_{15}H_{21}O_6N_5$ requires C, 49·0; H, 5·7; N, 19·1%). 2-n-*Butoxyethylamine*, b. p. 148—150°/22 mm. (Found: N, 11·4. $C_6H_{15}ON$ requires N, 11·9%); *picrolonate*, from ethanol, m. p. 172° (Found: C, 50·6; H, 5·6; N, 18·9. $C_{16}H_{23}O_6N_5$ requires C, 50·4; H, 6·0; N, 18·4%).

(6) *Secondary Monoamines containing Ether Groups.—Methyl-2-methoxyethylamine.* To methyl-2-methoxyethylaniline (165 g., 1 mol.), dissolved in concentrated hydrochloric acid (272 c.c.) and water (500 c.c.), sodium nitrite (74 g.) in water (125 c.c.) was added below 2°. After nitrosation was complete, the solution was added with stirring to a boiling solution of sodium hydroxide (275 g.) in water (5600 c.c.) in an iron pot arranged for distillation. Distillation was continued until the distillate was only faintly alkaline to brilliant-yellow paper. The total distillate was then acidified with hydrochloric acid, concentrated to 300 c.c., basified with 32% sodium hydroxide, and distilled to dryness. The amine was salted out from the distillate with sodium hydroxide, dried first over potassium hydroxide and then over sodium, and distilled; yield 45 g. (51%); b. p. 98—99°; *picrolonate*, from ethanol, m. p. 205° (Found: C, 48·3; H, 5·7; N, 20·0. $C_{14}H_{19}O_6N_5$ requires C, 47·8; H, 5·4; N, 19·8%). The following were made similarly: methyl-2-ethoxyethylamine (57%), b. p. 116—117°; ethyl-2-methoxyethylamine (64%), b. p. 117—119° [*picrolonate*, m. p. 222—223° (from ethanol) (Found: C, 49·0; H, 5·75. $C_{15}H_{21}O_6N_5$ requires C, 49·0; H, 5·7%)].

Ethyl-2-ethoxyethylamine. (*a*) The nitroso-compound (free base) was decomposed with sodium hydrogen sulphite as in the preparation of the diamines above; yield 20%; b. p. 129—130°. (*b*)* Ethyl bromide (109 g., 1 mol.), 2-ethoxyethylamine (220 g., 2·5 mols.), and water (50 c.c.) were heated in an autoclave at 90—100° for 24 hours; the mixture was then saturated with sodium hydroxide, and the amine isolated and distilled in the usual manner; yield 50 g., 42%; *picrolonate*, m. p. 181—182° (from ethanol) (Found: C, 50·25; H, 6·2; N, 18·9. $C_{16}H_{23}O_6N_5$ requires C, 50·3; H, 6·05; N, 18·4%).

*Di-(2-ethoxyethyl)amine.** (*a*) To a solution of di-(2-ethoxyethyl)aniline (116·2 g., 0·5 mol.) in concentrated hydrochloric acid (160 c.c.) and water (80 c.c.), sodium nitrite (40 g., 0·58 mol.) in water (100 c.c.) was added with stirring below 5°. Stirring was then continued for 30 minutes and concentrated aqueous ammonia was then added until the solution was alkaline to brilliant-yellow, and the nitroso-base was extracted with chloroform (100 c.c.). The extract was washed with water, dried (Na_2SO_4), and the chloroform removed by distillation under reduced pressure; 20% sodium hydrogen sulphite (2000 c.c.) was added to the residue, and the mixture was heated under reflux for 2 hours. The whole was then acidified to Congo-red with concentrated hydrochloric acid, concentrated to approximately 1500 c.c., basified with sodium hydroxide, and steam-distilled until the distillate was only faintly alkaline to brilliant-yellow. The distillate (6 l.), after being acidified with hydrochloric acid, was evaporated to dryness, and the residue was basified with sodium hydroxide and extracted with ether after saturation with solid sodium hydroxide. The ether extract after drying over potassium hydroxide was fractionated, giving 22 g. (27·5%) of di-(2-ethoxyethyl)amine, b. p. 198—200°; *picrolonate*, from ethanol, m. p. 161° (Found: C, 51·4; H, 6·55; N, 16·9. $C_{18}H_{27}O_7N_5$ requires C, 50·9; H, 6·35; N, 16·5%).

(*b*) 2-Ethoxyethyl chloride (108 g., 1 mol.), 2-ethoxyethylamine (200 g., 1·7 mols.), and water (25 c.c.) were heated under reflux for 20 hours. After cooling, the solution was saturated with sodium

TABLE II.

Alkylenediamines, NHR·[CH$_2$]$_n$·NHR′.

R = R′.	*n*.	Method of prepn.	Yield, %.	B. p.	M. p. of dihydrochloride.	Solvent.‡	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me	2	A	80	120°	235° (d.)								
		B	75										
		C	15										
Me (Et) [1]	2	B	44	135	235								
Et	2	A	80	151—152	266								
		B	50										
Pr$^{\alpha}$	2	A	91	186—189	300 (d.)	W–A	$C_8H_{22}N_2Cl_2$	44·4	9·6	—	44·3	10·1	—
Pr$^{\beta}$	2	A	0	169—171	250 (d.)	E–A	$C_8H_{22}N_2Cl_2$	44·8	10·1	12·6	44·3	10·1	12·8
		B	0										
		C	38										
Allyl	2	A	0	198—200	250 (d.)	EtOH	$C_8H_{18}N_2Cl_2$	44·8	8·5	13·2	45·1	8·5	13·2
		C	41										
n-Bu	2	A	80	226—228	295—300(d.)	W–A	$C_{10}H_{26}N_2Cl_2$	48·7	10·2	—	49·0	10·6	—
iso-Bu	2	A	90	212—214	285 (d.) †	EtOH	$C_{10}H_{26}N_2Cl_2$			29·1 §			29·0 §
		C	57										
sec.-Bu	2	C	51	210	187	E–A	$C_{10}H_{26}N_2Cl_2$	—	—	11·5	—	—	11·4
tert.-Bu	2	C	42	196—198	275—280 (d.)	E–A	$C_{10}H_{26}N_2Cl_2$	49·4	11·0	—	49·0	10·6	—
*cyclo*Hexyl	2	C	78	312	265	EtOH	$C_{14}H_{30}N_2Cl_2$	56·8	9·95	9·2	56·5	10·1	9·4
C_2H_4·OMe	2	C	44	240—241	196	E–A	$C_8H_{20}O_2N_2Cl_2$	38·5	8·7	—	38·5	8·8	—
C_2H_4·OEt	2	C	50	256—258	212	E–A	$C_{10}H_{24}O_2N_2Cl_2$	43·0	8·7	9·7	43·3	9·3	10·1
C_2H_4·OPr$^{\beta}$	2	C	33	—	231	E–A	$C_{12}H_{30}O_2N_2Cl_2$	47·6	9·95	9·4	47·3	9·8	9·2
Me	3	B	80	145	266	EtOH	$C_5H_{16}N_2Cl_2$	34·7	9·2	15·7	34·3	9·15	15·9
Me (Et) [1]	3	B	72	158	270	,,	$C_6H_{18}N_2Cl_2$	—	—	14·75	—	—	14·8
Et	3	B	46	170—173	>300	,,	$C_7H_{20}N_2Cl_2$	41·7	9·8	35·4 §	41·7	9·85	35·0 §
Pr$^{\alpha}$	3	A	68	212—216	300	E–A	$C_9H_{24}N_2Cl_2$	47·6	10·5	—	47·2	10·4	—
Me	4	A	70	164	275 (d.)	W–E	$C_6H_{18}N_2Cl_2$	37·9	9·5	14·4	38·1	9·5	14·8
Me	5	A	41	190	254 (d.)	E–A	$C_7H_{20}N_2Cl_2$	41·2	9·7	—	41·2	9·8	—
Me	6	A	80	205	210	E–A	$C_8H_{22}N_2Cl_2$	43·9	9·9	12·8	44·1	10·1	12·8
Et	6	A	77	228	278	EtOH	$C_{10}H_{26}N_2Cl_2$	48·6	10·9	—	48·8	10·6	—
C_2H_4·OEt	6	C	30	190—193 /18 mm.	262 (d.)	,,	$C_{14}H_{34}O_2N_2Cl_2$	50·8	10·5	8·7	50·5	10·2	8·4

[1] In these two compounds R = Me, R′ = Et.
† Rameau (*Rec. Trav. chim.*, 1938, **57**, 206) gives m. p. 130° for this hydrochloride.
‡ W–A = Water–acetone; E–A = ethanol–acetone; W–E = water–ethanol.
§ These data refer to Cl.

hydroxide, and the base layer separted, dried over potassium hydroxide, and distilled, giving 98 g. (61%) of di-(2-ethoxyethyl)amine.

(7) *Biscarbamyl Chlorides and Cyclic Ureas.*—The experiments in this section, in which a diamine was treated with carbonyl chloride, were designed to give the biscarbamyl chlorides as well as the cyclic ureas.

1 : 3-*Dimethyliminazolid-2-one and* NN′-*dimethylethylenediamine*-NN′-*dicarboxychloride.* To a solution of carbonyl chloride (170 g.) in toluene (1000 c.c.), a solution of *NN′*-dimethylethylenediamine (145 g.) in toluene (500 c.c.) was added with stirring below − 15°. The excess of carbonyl chloride was then removed by a stream of dry air, and the amine hydrochloride was filtered off and washed with chloroform. The combined filtrate and washings were then distilled, giving 30 g. of crude 1 : 3-dimethyliminazolid-2-one, b. p. 129°/39 mm., and an undistillable residue of *NN′*-dimethylethylenediamine-*NN′*-dicarboxychloride. The first fraction was dissolved in water (100 c.c.), and the solution saturated with potassium carbonate and extracted with chloroform. After drying (K_2CO_3), the extract was distilled, giving 24 g. of 1 : 3-*dimethyliminazolid-2-one*, b. p. 104°/15 mm. (Found: C, 52·4; H, 8·55; N, 24·4. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·5%).

The following were made similarly: 1 : 3-*diethyliminazolid-2-one*, b. p. 122°/22 mm. (Found: C, 58·9; H, 10·2; N, 19·4. $C_7H_{14}ON_2$ requires C, 59·1; H, 9·9; N, 19·7%), and *NN′*-diethylethylenediamine-*NN′*-dicarboxychloride from *NN′*-diethylethylenediamine; 1 : 3-*di*-n-*propyliminazolid-2-one*, b. p. 148°/23 mm. (Found: C, 63·4; H, 10·7; N, 16·2. $C_9H_{18}ON_2$ requires C, 63·5; H, 10·6; N, 16·4%), and the dicarboxychloride from *NN′*-di-*n*-propylethylenediamine; the iso*propylurea*, b. p. 130°/15 mm. (Found: C, 63·45; H, 10·1. $C_9H_{18}ON_2$ requires C, 63·5; H, 10·6%), and NN′-*diiso*propyl-*ethylenediamine*-NN′-*dicarboxychloride*, m. p. 110° (from petrol, b. p. 60—80°) (Found: C, 45·0; H, 6·45. $C_{10}H_{18}O_2N_2Cl_2$ requires C, 44·7; H, 6·7%), from *NN′*-di*iso*propylethylenediamine; 1 : 3-*dimethylhexahydropyrimid-2-one*, b. p. 146°/44 mm. (Found: C, 55·9; H, 9·1; N, 21·4. $C_6H_{12}ON_2$ requires C, 56·2; H, 9·3; N, 21·8%), and *NN′*-dimethyltrimethylenediamine-*NN′*-dicarboxychloride, b. p. 163—166°/0·8 mm. (decomp.), from *NN′*-dimethyltrimethylenediamine.

(8) *Ureas of Type* X·CO·NR·$[CH_2]_n$·NHR, *where* X *is a Secondary Amine Residue.*—*Triethyl-2-ethylaminoethylurea and* NN′-*diethylethylenediamine*-NN′-*biscarboxydiethylamide.* To *NN′*-diethylethylenediamine (48 g., 0·4 mol.) in toluene (450 c.c.), diethylcarbamyl chloride (50 g., 0·41 mol.) in toluene (300 c.c.) was added below 0° with stirring which was continued for 1 hour after addition was complete. The diamine dihydrochloride was filtered off, and the filtrate shaken with saturated potassium carbonate (200 c.c.). After drying (K_2CO_3), the toluene solution was distilled, giving 23 g. of crude *triethyl-2-ethylaminoethylurea* [which redistilled giving 14 g., b. p. 126—8°/17 mm. (Found: N, 19·0. $C_{11}H_{25}ON_3$ requires N, 19·5%)] and 38 g. of NN′-*diethylethylenediamine*-NN′-*biscarboxydiethylamide*, b. p. 218°/19 mm. (Found: C, 61·7; H, 11·0; N, 17·7. $C_{16}H_{34}O_2N_4$ requires C, 61·2; H, 10·8; N, 17·8%).

The following were obtained by a similar procedure: N-*Methyl*-N′N′-*diethyl*-N-3-*methylaminopropylurea*, b. p. 141°/10 mm. (Found: N, 20·5. $C_{10}H_{23}ON_3$ requires N, 20·9%), and NN′-*dimethyltrimethylenediamine*-NN′-*biscarboxydiethylamide*, b. p. 210°/10 mm., 160°/0·7 mm. (Found: C, 60·2; H, 10·45; N, 18·4. $C_{15}H_{32}O_2N_4$ requires C, 60·0; H, 10·65; N, 18·6%), from *NN′*-dimethyltrimethylenediamine and diethylcarbamyl chloride; N-*methyl*-N′N′-*diethyl*-N-6-*methylamino*-n-*hexylurea*, b. p. 182°/12 mm. (Found: C, 63·7; H, 11·75; N, 17·1. $C_{12}H_{29}ON_3$ requires C, 64·2; H, 11·8; N, 17·3%), and NN′-*dimethylhexamethylenediamine*-NN′-*biscarboxydiethylamide*, b. p. 229—230°/9 mm. (Found: C, 63·05; H, 10·9. $C_{18}H_{38}O_2N_4$ requires C, 63·1; H, 11·1%), from *NN′*-dimethylhexamethylenediamine and diethylcarbamyl chloride; NN-*pentamethylene*-N′-2-*ethoxyethyl*-N′-(2-*ethoxyethylaminoethyl*)*urea*, b. p. 180°/15 mm. (Found: C, 60·6; H, 10·3; N, 12·9. $C_{16}H_{33}O_3N_3$ requires C, 60·95; H, 10·5; N, 13·3%), and *NN′*-di-(2-ethoxyethyl)ethylenediamine-*NN′*-biscarboxypiperidide, b. p. 275—278°/15 mm. (the yield of bis-urea was much smaller in the last case).

(9) *Preparation of Bisureas of Type* X·CO·NR·$[CH_2]_n$·NR′·COX *in which* R *and* R′ *are Alkyl, Alkenyl, or Alkoxyethyl Groups and* X *is a Secondary Amine Residue.*[1]—(A) *Reaction of a biscarbamyl chloride* COCl·NR·$[CH_2]_n$·NR′·COCl *with a secondary amine.* To the biscarbamyl chloride (1 mol.) dissolved in dry benzene the secondary amine (5 mols.) was added with shaking and cooling. After standing overnight, the precipitated amine hydrochloride was filtered off, and the filtrate shaken with saturated aqueous potassium carbonate, dried (K_2CO_3), and distilled.

(B) *Reaction of a diamine* NHR·$[CH_2]_n$·NHR′ *with a carbamyl chloride.* To the diamine (1 mol.) in benzene the carbamyl chloride (1·1 mols.) was added. Precipitation of the diamine hydrochloride began almost immediately and was accompanied by a rise in temperature. After standing overnight, the diamine hydrochloride was filtered off and the bisurea isolated as above.

Details of the various preparations are given in Table III. The solvent used for crystallisation of solids was usually petrol (b. p. 60—80°), but in a few cases that of b. p. 40—60° was used.

(10) *Bisureas of Type* X·CO·NR·$[CH_2]_n$·NR·COY.—These substances were made by reaction of a monourea of type X·CO·NR·$[CH_2]_n$·NHR (see above) with the appropriate carbamyl chloride, either without a solvent or in a solvent heated under reflux. Details of the preparation of NN′-*dimethyltrimethylenediamine-N-carboxydiethylamide-N′-carboxypiperidide* are given in illustration: *N*-Methyl-*NN′*-diethyl-*N*-3-methylaminopropylurea (25 g., 1·25 mols.) and piperidine-*N*-carboxychloride (10 g., 0·68 mol.) were mixed; much heat was evolved and when the temperature had fallen to 30° the mixture was heated for 2 hours on the boiling water-bath, poured into water, the aqueous solution saturated with potassium carbonate, and extracted with benzene. After being dried (K_2CO_3), the benzene solution was distilled, giving 6 g. of unchanged monourea and 15 g. (78%) of the *bisurea*, b. p. 245°/17 mm. (Found: C, 61·4; H, 10·3; N, 18·0. $C_{16}H_{33}O_2N_4$ requires C, 61·5; H, 10·3; N, 18·15%), as a pale yellow oil soluble to the extent of about 25% in water.

The following were prepared similarly: NN′-*Dimethylhexamethylenediamine*-N-*carboxydiethylamide*-

[1] The preparation of bisureas is covered by B.PP. 548,625, 548,626, 560,681, 560,699, 560,700, and 560,701.

TABLE III.

Bisureas X·CO·NR·[CH$_2$]$_n$·NR′·CO·X.

X.	R.	R′.	*n*.	Method of prepn.	Yield, %.	M. p.[1]	S.†	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Me_2N	Me	Me	2	B	48	(193—195°/20 mm.)	Misc.	$C_{10}H_{12}O_2N_4$	52·1	9·6	23·95	52·1	9·56	24·2
Et_2N	Me	Me	2	A B	90	339° (224°/13 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·2	10·35	19·7	58·6	10·5	19·6
O<[CH$_2$]$_4$>N	Me	Me	2	B	75	164°	>50%	$C_{14}H_{26}O_4N_4$	53·55	8·3	—	53·5	8·3	—
Me_2N	Me	Et	2	B	72	(204—205°/22 mm.)	Misc.	$C_{11}H_{24}O_2N_4$	53·95	9·5	23·2	54·0	9·8	22·9
Et_2N	Me	Et	2	B	67	(204°/10 mm.)	Misc.	$C_{15}H_{32}O_2N_4$	59·8	10·3	18·8	60·0	10·6	18·7
[CH$_2$]$_5$>N	Me	Et	2	B	83	(252—254°/6 mm.)	2%	$C_{17}H_{32}O_2N_4$	62·9	10·0	17·6	62·9	9·9	17·3
O<[CH$_2$]$_4$>N	Me	Et	2	B	50	76°	>50%	$C_{15}H_{28}O_4N_4$	54·5	8·2	16·75	54·8	8·5	17·0
Me_2N	Et	Et	2	B	85	(203—205°/23 mm.)	Misc.	$C_{12}H_{26}O_2N_2$	55·9	10·15	—	55·8	10·1	—
Et_2N	Et	Et	2	B	85	(226—228°/29 mm.)	20%	$C_{16}H_{34}O_2N_4$	61·4	11·0	17·7	61·2	10·8	17·8
[CH$_2$]$_5$>N	Et	Et	2	B	50	65°	< 5%	$C_{18}H_{34}O_2N_4$	63·7	9·85	16·2	63·7	10·0	16·6
O<[CH$_2$]$_4$>N	Et	Et	2	B	68	98°	>50%	$C_{16}H_{34}O_4N_4$	56·3	8·8	16·2	56·1	8·8	16·4
NEt·C_2H_4·OMe	Et	Et	2	A	75	(239—240°/17 mm.)	Misc.	$C_{18}H_{38}O_4N_4$	57·3	9·9	15·2	57·6	10·15	15·0
Me_2N	Pr$^\alpha$	Pr$^\alpha$	2	B	65	(208—209°/18 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·4	10·1	19·55	58·7	10·5	19·7
O<[CH$_2$]$_4$>N	Pr$^\alpha$	Pr$^\alpha$	2	B	33	86°	>50%	$C_{18}H_{34}O_4N_4$	58·7	9·25	15·15	58·3	9·2	15·15
NMe·C_2H_4·OEt	Pr$^\alpha$	Pr$^\alpha$	2	A	46	(255°/20 mm.)	>50%	$C_{20}H_{42}O_4N_4$	59·3	10·3	13·8	59·6	10·4	13·9
NEt·C_2H_4·OMe	Pr$^\alpha$	Pr$^\alpha$	2	A	58	(265°/20 mm.)	50%	$C_{20}H_{42}O_4N_4$	59·4	10·3	13·8	59·6	10·4	13·9
Me_2N	Pr$^\beta$	Pr$^\beta$	2	B	40	100°(202°/17 mm)	50%	$C_{14}H_{30}O_2N_4$	58·6	10·4	19·7	58·7	10·5	19·7
O<[CH$_2$]$_4$>N	Pr$^\beta$	Pr$^\beta$	2	B	29	126°	>50%	$C_{18}H_{34}O_4N_4$	57·8	9·1	15·1	58·3	9·2	15·15
Me_2N	Allyl	Allyl	2	B	80	(220°/20 mm.)	Misc.	$C_{14}H_{26}O_2N_4$	59·55	9·15	19·9	59·6	9·2	19·9
O<CH_2]$_4$>N	Allyl	Allyl	2	B	77	85°	>50%	$C_{18}H_{30}O_4N_4$	59·0	7·9	15·7	59·0	8·2	15·3
Me_2N	*n*-Bu	*n*-Bu	2	B	68	(222—224°/18 mm.)	10%	$C_{16}H_{34}O_2N_4$	61·16	10·75	17·85	61·1	10·8	17·8
O<[CH$_2$]$_4$>N	*n*-Bu	*n*-Bu	2	B	60	41°	50%	$C_{20}H_{38}O_4N_4$	60·3	9·55	13·9	60·3	9·55	14·1
$(EtO·C_2H_4)_2N$*	*n*-Bu	*n*-Bu	2	B	—	(240—245°/12 mm.)	>50%	$C_{28}H_{58}O_6N_4$	61·9	11·0	10·4	61·5	10·6	10·3
Me_2N	*iso*-Bu	*iso*-Bu	2	B	97	(220°/30 mm.)	10%	$C_{16}H_{34}O_2N_4$	61·5	10·6	17·7	61·1	10·8	17·8
O<[CH$_2$]$_4$>N	*iso*-Bu	*iso*-Bu	2	B	56	(270—275°/15 mm.)	20%	$C_{20}H_{38}O_4N_4$	60·7	9·55	—	60·3	9·55	—
Me_2N	*sec.*-Bu	*sec.*-Bu	2	B	38	105° (232—234°/40 mm.)	<10%	$C_{16}H_{34}O_2N_4$	61·35	10·4	17·4	61·1	10·8	17·8
O<[CH$_2$]$_4$>N	*sec.*-Bu	*sec.*-Bu	2	B	30	135°	10%	$C_{20}H_{38}O_4N_4$	—	—	13·6	—	—	14·1

O<[CH$_2$]$_4$>N	*tert.*-Bu	*tert.*-Bu	2	B	9	132°	10%	$C_{20}H_{38}O_4N_4$	—	—	14·5	—	—	14·1
O<[CH$_2$]$_4$>N	*cyclo*Hexyl	*cyclo*Hexyl	2	B	25	148°	<10%	$C_{24}H_{42}O_4N_4$	—	—	12·6	—	—	12·4
Et$_2$N	2-MeO·C$_2$H$_4$	2-MeO·C$_2$H$_4$	2	B	50	(252°/23 mm.)	20%	$C_{16}H_{34}O_4N_4$	57·5	10·4	14·75	57·8	10·15	14·95
[CH$_2$]$_5$>N	2-MeO·C$_2$H$_4$	2-MeO·C$_2$H$_4$	2	B	54	(285°/17 mm.)	<10%	$C_{20}H_{38}O_4N_4$	60·7	9·55	13·92	60·3	9·55	14·05
O<[CH$_2$]$_4$>N	2-Pr$^\beta$O·C$_2$H$_4$	2-Pr$^\beta$O·C$_2$H$_4$	2	B	53	94°	50%	$C_{22}H_{42}O_6N_8$	57·8	9·1	—	57·8	9·2	—
Me$_2$N	Me	Me	3	B	56	(213°/24 mm.)	Misc.	$C_{11}H_{24}O_2N_4$	54·1	9·6	22·85	54·1	9·8	22·9
Et$_2$N	Me	Me	3	B	88	(160°/0·7 mm.; 225°/21 mm.)	Misc.	$C_{15}H_{32}O_2N_4$	60·2	10·45	18·4	60·0	10·7	18·6
NMePr$^\alpha$	Me	Me	3	A	57	(225°/16 mm.)	10%	$C_{15}H_{32}O_2N_4$	59·0	10·3	18·6	60·0	10·7	18·6
NMePr$^\beta$	Me	Me	3	A	60	(218°/15 mm.)	5%	$C_{15}H_{32}O_2N_4$	60·35	10·85	18·1	60·0	10·7	18·6
[CH$_2$]$_6$>N	Me	Me	3	B	73	(205°/0·75 mm.)	< 5%	$C_{17}H_{32}O_2N_4$	62·5	10·2	17·3	62·8	9·9	17·3
O<[CH$_2$]$_4$>N	Me	Me	3	B	60	93°	>50%	$C_{16}H_{32}O_4N_4$	55·3	8·4	17·0	55·0	8·5	17·1
NMe·C$_2$H$_4$·OMe ...	Me	Me	3	A	61	(253°/16 mm.)	Misc.	$C_{16}H_{32}O_4N_4$	54·45	9·55	16·95	54·2	9·6	16·9
NMe·C$_2$H$_4$·OEt ...	Me	Me	3	A	61	(258°/15 mm.)	>50%	$C_{17}H_{34}O_4N_4$	57·0	10·4	15·65	56·7	10·0	15·6
NEt·C$_2$H$_4$·OMe ...	Me	Me	3	A	61	(254°/19 mm.)	Misc.	$C_{17}H_{34}O_4N_4$	56·2	9·95	15·9	56·7	10·0	15·6
NEt·C$_2$H$_4$·OEt ...	Me	Me	3	A	49	(253°/14 mm.)	>50%	$C_{19}H_{40}O_4N_4$	58·5	10·15	14·55	58·7	10·3	14·45
Me$_2$N	Me	Et	3	B	84	(219°/21 mm.)	Misc.	$C_{12}H_{26}O_2N_4$	55·45	9·8	21·65	55·7	10·05	21·7
Et$_2$N	Me	Et	3	B	75	(219°/12 mm.)	10%	$C_{16}H_{34}O_2N_4$	60·9	10·5	18·1	61·1	10·8	17·8
[CH$_2$]$_5$>N	Me	Et	3	B	51	(256°/14 mm.)	< 5%	$C_{15}H_{34}O_2N_4$	63·6	10·5	—	63·8	10·1	—
O<CH$_2$]$_4$>N	Me	Et	3	B	52	(236—238°/1·7 mm.)	Misc.	$C_{14}H_{30}O_4N_4$	56·1	8·65	16·1	56·1	8·8	16·3
Et$_2$N	Et	Et	3	B	56	(244—246°/40 mm.)	<10%	$C_{17}H_{36}O_2N_4$	62·4	10·8	16·6	62·2	11·0	17·0
[CH$_2$]$_5$>N	Et	Et	3	B	50	(223—225°/0·6 mm.)	< 5%	$C_{19}H_{36}O_2N_4$	64·5	10·1	15·95	64·6	10·2	15·9
O<[CH$_2$]$_4$>N	Et	Et	3	B	56	(238—240°/0·7 mm.)	10%	$C_{17}H_{32}O_4N_4$	56·8	9·15	15·2	57·2	9·0	15·9
Me$_2$N	Pr$^\alpha$	Pr$^\alpha$	3	B	30	(220°/16 mm.)	5%	$C_{15}H_{32}O_2N_4$	60·1	10·4	—	60·0	10·65	—
O<[CH$_2$]$_4$>N	Pr$^\alpha$	Pr$^\alpha$	3	B	40	(287°/18 mm.)	5%	$C_{19}H_{36}O_4N_4$	59·2	9·45	14·2	59·3	9·1	14·6
Et$_2$N	Me	Me	4	B	90	(216°/10 mm.)	>50%	$C_{16}H_{34}O_2N_4$	61·6	11·3	18·0	61·1	10·9	17·9
Et$_2$N	Me	Me	5	B	75	(270—275°/50 mm.)	50%	$C_{17}H_{36}O_2N_4$	61·95	10·65	17·35	62·1	10·95	17·1
Me$_2$N	Me	Me	6	B	28	(238—240°/17 mm.)	Misc.	$C_{14}H_{30}O_2N_4$	58·5	9·9	19·8	58·7	10·4	19·7
Et$_2$N	Me	Me	6	B	61	(252—254°/18 mm.)	50%	$C_{18}H_{38}O_2N_4$	63·1	10·9	—	63·1	11·1	—
O<[CH$_2$]$_4$>N	Me	Me	6	B	50	93—94°	50%	$C_{18}H_{34}O_4N_4$	57·8	9·7	14·8	58·3	9·2	15·1
Me$_2$N	Et	Et	6	B	90	(242—244°/2 mm.)	50%	$C_{16}H_{34}O_2N_4$	61·2	10·5	17·95	61·2	10·8	17·85
O<[CH$_2$]$_4$>N	Et	Et	6	B	83	(315°/24 mm.)	>50%	$C_{20}H_{38}O_4N_4$	—	—	13·7	—	—	14·0
Me$_2$N *	2-EtO·C$_2$H$_4$	2-EtO·C$_2$H$_4$	6	B	60	(268—269°/11 mm.)	Misc.	$C_{20}H_{42}O_4N_4$	60·0	10·6	14·1	59·7	10·5	14·0

[1] B. p.'s are given in parentheses.
† *S* = Solubility (approx.) in water (Misc. = miscible in all proportions).

N'-carboxymorpholide, b. p. 248°/9 mm., yield 75%, miscible with water (Found: C, 61·1; H, 9·95; N, 15·9. $C_{10}H_{18}O_3N_4$ requires C, 60·7; H, 10·1; N, 15·7%) from *N*-methyl-*N'N'*-diethyl-*N*-6-methylaminohexylurea and morpholine-*N*-carboxychloride; *NN'-di-(2-ethoxyethyl)ethylenediamine-N-carboxydimethylamide-N'-carboxypiperidide*, b. p. 230°/10 mm., yield 47%, solubility in water >50% (Found: C, 58·8; H, 9·75; N, 14·8. $C_{19}H_{38}O_4N_4$ requires C, 59·1; H, 9·8; N, 14·5%), and *NN'-di-(2-ethoxyethyl)-ethylenediamine-N-carboxy(ethyl-2-ethoxyethyl)amide-N'-carboxypiperidide* b. p. 245—247°/10 mm., 21% yield, miscible with water (Found: C, 59·9; H, 10·0; N, 11·95. $C_{23}H_{46}O_5N_4$ requires C, 60·25; H, 10·0; N, 12·2%), from *NN*-pentamethylene-*N'*-2-ethoxyethyl-*N'*-2-(2-ethoxyethylamino)ethylurea and dimethylcarbamyl chloride and ethyl-(2-ethoxyethyl)carbamyl chloride, respectively.

RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
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59. *The Thermal Decomposition of 2 : 2'-Dichlorodiethyl Sulphide.*

By A. H. WILLIAMS.

The thermal decomposition of 2 : 2'-dichlorodiethyl sulphide ("mustard gas") has been investigated at various temperatures. The main products isolated were hydrogen chloride, ethylene, ethylene dichloride, dithian, and 2 : 2'-dichlorodiethyl disulphide; at the highest temperatures hydrogen sulphide and vinyl chloride were found in addition. Decomposition appears to be complete at 450°.

IN spite of the military use of 2 : 2'-dichlorodiethyl sulphide and the large amount of work carried out on its preparation and properties, there is but little information on the products of its thermal decomposition. Bell, Bennett, and Hock (*J.*, 1927, 1805) note the formation of dithian and ethylene dichloride when the substance is heated in a sealed tube at 180° for 18 hours. Sartori ("The War Gases", p. 226) states that decomposition commences at about 150° and is complete at 500°, with evolution of hydrogen chloride and "toxic and lachrymatory gases", but gives no reference to the source of this information.

In the present investigation a qualitative and roughly quantitative determination has been made of the products, the nature and proportions of which vary with the temperature of heating. Decomposition in the liquid phase was followed by heating under reflux for two hours in a constant-temperature bath; the temperatures chosen were 180°, the lowest temperature at which decomposition proceeds at a reasonable rate, and the boiling point, which is about 220° at atmospheric pressure. The vapour-phase decomposition was investigated at 350° and 450°, the liquid being dropped into a heated packed column at the rate of about 1 ml./min.

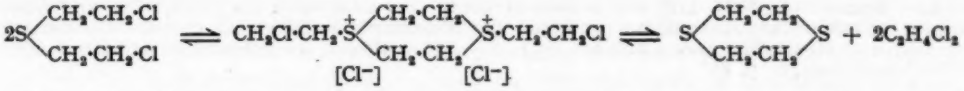
The results are conveniently summarised in the following table; the yields of the various products are expressed as percentages of the initial weight of 2 : 2'-dichlorodiethyl sulphide used.

Temp.	180°.	B. p. (*ca.* 220°).	350°.	450°.
Hydrogen chloride	8·0	21·2	25·8	31·5
Ethylene	4·2	11·2	7·9	10·4
Ethylene dichloride	6·9	11·1	—	—
Hydrogen sulphide	—	—	3·9	5·2
Vinyl chloride	—	—	14·6	19·4
Dithian	1·3	3·3	Trace	Trace
2 : 2'-Dichlorodiethyl disulphide	5·8	8·5	2·0	—
2 : 2'-Dichlorodiethyl sulphide recovered	56·0	14·2	13·0	—
Non-volatile residue	12·2	25·7	*ca.* 31	*ca.* 32 (by difference)
Carbon disulphide	—	—	*ca.* 1	*ca.* 1

The non-volatile residue from the 180° and the b. p. run, left after heating at 120°/4 mm., gave an average analysis of S, 43—44; Cl, 17—17·5%. The residue from the higher-temperature runs, being distributed over the interior of the column, was not available for analysis, but a survey of the products at 450° shows that it too must have a high sulphur and an even lower chlorine content since the characterised products leave only about 7% of the chlorine but 45% of the sulphur unaccounted for.

The principal decomposition product, hydrogen chloride, was to be expected in the thermal decomposition of an organic chloride. The exclusive formation of ethylene and complete absence of acetylene is interesting; possibly there is a reversal of the direct formation of 2 : 2'-dichlorodiethyl sulphide from ethylene and sulphur chlorides, for in the presence of excess of the chloro-sulphide at the high temperature any sulphur chlorides formed would be quickly destroyed with liberation of hydrogen chloride and formation of high-molecular-weight products such as occur in the non-volatile residue.

Ethylene dichloride and dithian were found, as expected from the results of Bell, Bennett, and Hock (*loc. cit.*), whose theory of an intermediate sulphonium complex accounts satisfactorily for the formation of these products :



The yield of dithian was, however, smaller than expected and less than corresponds to the ethylene dichloride formed by the above reaction : the sulphonium complex, however, need not be only of the simple cyclic type shown but may equally well be of chain form, giving the non-volatile polymeric ethylene sulphide along with ethylene dichloride. The above workers carried out the decomposition in a sealed tube at 180° and obtained a 50% yield of dithian. Repetition of the experiment under their conditions gave yields of only 10% of dithian with considerable amounts of ethylene and hydrogen chloride : they did not record the formation of these gaseous products, whose presence is obvious on opening the sealed tube.

The formation of 2 : 2′-dichlorodiethyl disulphide is rather surprising, as it is less stable to heat than is the monosulphide.

A sharp division exists between the products at the two higher temperatures and the two lower. Hydrogen sulphide and vinyl chloride are formed at the higher temperatures, but no vinyl chloride and only a trace of hydrogen sulphide were found at the lower temperatures. Conversely, ethylene dichloride appears only at the lower temperatures, and the yield of ethylene relative to hydrogen chloride falls noticeably at the higher temperatures. These changes may be due in part to the change from glass to silica as the material of the reaction vessel; the introduction of silica rings into the decomposition at the b. p. did not produce any vinyl chloride but gave a small quantity of hydrogen sulphide and some acceleration of the normal reaction. Packing of the reaction vessel with glass-wool at this temperature gave no significant change, so the decomposition in glass at the b. p. is not a surface reaction : some surface reaction occurs on silica, though without appreciable change in the proportion of the products. These results are summarised in tabular form :

Effect of glass-wool and silica on decomposition at the boiling point : Products, %.

	Normal reaction.	With silica.	With glass-wool.
HCl	21·2	28·8	19·7
C_2H_4	11·2	14·4	10·8
H_2S	0	0·4	0

The reaction at 350° and 450° will take place largely in the vapour state, and this may well be the real cause of the difference in products. The persistence of some products from the lower-temperature liquid-phase reaction is to be expected as the material enters the column in liquid form.

It is noteworthy that the molecular ratio of hydrogen sulphide to vinyl chloride is almost exactly 1 : 2 at both temperatures; their formation would appear to be due to the simple reaction $S(CH_2{\cdot}CH_2Cl)_2 \longrightarrow H_2S + 2CH_2{:}CHCl$.

Experimental.

All decompositions were carried out in an atmosphere of nitrogen. For the runs at 180° and the b. p., the material was heated under a reflux air condenser in a flask immersed in an oil-bath; a slow stream of nitrogen was bubbled through to carry over volatile products. In the higher-temperature runs the nitrogen stream passed through the electrically heated quartz column packed with quartz rings down which the chloro-sulphide was dropped.

The volatile products were passed through a trap cooled in alcohol–solid carbon dioxide (− 78°), followed by bubblers containing water, alkali, and bromine-water successively to collect hydrogen chloride, hydrogen sulphide, and ethylene. At the end of a run, the apparatus was flushed out with nitrogen, then the bromine-water bubblers were replaced by fresh ones and the cold trap was allowed to warm to room temperature : vinyl chloride (b. p. − 14°) and dissolved hydrogen chloride and sulphide were then swept through and collected in the appropriate reagents.

Hydrogen chloride was collected in water and estimated by direct titration. Hydrogen sulphide was absorbed in sodium hydroxide solution and estimated as sulphide by iodine–thiosulphate titration. Ethylene was absorbed in bromine-water, and the ethylene dibromide collected and weighed after being washed with dilute alkali and water, and dried; its purity was checked by distillation. Ethylene dichloride was recovered from the cold trap and treated similarly. Vinyl chloride collected in the cold trap, and when this was allowed to warm, the chloride evaporated and was collected in bromine-water; the resulting 1-chloro-1 : 2-dibromoethane was separated, washed, dried, and weighed, and its purity checked by fractionation.

A small amount of carbon disulphide was found in the cold trap after evaporation of the vinyl chloride from runs at 350° and 450° : the amount was too small for accurate determination.

2 : 2′-Dichlorodiethyl disulphide was found on fractionation of the residual material; b. p. 110°/4 mm. (slight decomp.); the analysis was poor (Found : S, 33·9; Cl, 36·3. Calc. for $C_4H_8Cl_2S_2$: S, 33·55; Cl, 37·1%). Bennett (*J.*, 1921, **119**, 424) records similarly poor analysis of his preparation, and further work by the author (unpublished) has confirmed the difficulty of obtaining good figures. Condensation with 2-hydroxyethanethiol gave a product, m. p. 81—82° *ex* alcohol, undepressed by admixture with a synthetic specimen, m. p. 81°.

The author is indebted to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this paper.

CHEMICAL DEFENCE RESEARCH ESTABLISHMENT,
SUTTON OAK, ST. HELENS, LANCASHIRE.

[*Received, June 17th*, 1946.]

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60. *Some Aliphatic Thiols and their Derivatives. Part I. Aliphatic Mercaptoamines.*

By JOHN HARLEY-MASON.

In this paper the preparation and properties of four aliphatic 2-mercaptoamines are described. All were obtained from the corresponding chloroamines by reaction with thiourea and decomposition of the resulting *iso*thiouronium salts with alkali.

ALTHOUGH many aliphatic hydroxyamines are well known and are commercially available, little work has been recorded on the corresponding mercaptoamines. 2-Aminoethylthiol has long been known (Gabriel, *Ber.*, 1891, **24**, 1111; see also Mills and Bogert, *J. Amer. Chem. Soc.*, 1940, **62**, 1173), and 2-diethylaminoethylthiol has recently been prepared (Albertson and Clinton, *ibid.*, 1945, **67**, 1222), but other compounds of this type, and, in particular, amines containing two or more thiol groups, have not hitherto been described. In the present paper the preparation and properties of 2 : 2′-*dimercapto-diethylamine* (I) and *-triethylamine* (II), *methyl*-2 : 2′-*dimercaptodiethylamine* (III), and 2 : 2′ : 2″-*trimercaptotriethylamine* (IV) are described.

$NH(CH_2{\cdot}CH_2{\cdot}SH)_2$ (I.) $NEt(CH_2{\cdot}CH_2{\cdot}SH)_2$ (II.) $NMe(CH_2{\cdot}CH_2{\cdot}SH)_2$ (III.) $N(CH_2{\cdot}CH_2{\cdot}SH)_3$ (IV.)

All of these were prepared from the corresponding hydroxy-compounds (ethanolamines) which were first converted into the chloroamines by means of thionyl chloride. The chloroamines or their hydrochlorides reacted with thiourea in boiling ethanol to give hydrochlorides of *iso*thiourea derivatives, which on basification and warming gave the required thiols and dicyanodiamide (cf. Arndt, *Ber.*, 1921, **54**, 2236; Hall and Reid, *J. Amer. Chem. Soc.*, 1943, **65**, 1466). Three of the four *iso*thiourea derivatives, *ethyl-* and *methyl-di-*(2-iso*thioureido*-S-*ethyl*)*amine trihydrochloride* and *tri-*(2-iso*thioureido*-S-*ethyl*)*amine tetrahydrochloride*, were well crystalline, sparingly soluble in alcohol, and very soluble in water. The free bases corresponding to these salts were also exceedingly soluble in water and no attempt was made to isolate them. When the hydrochlorides of the *iso*thiourea derivatives were treated in aqueous solution with sodium hydroxide in slight excess over that required to neutralise the hydrochloric acid, and the whole heated on the water-bath, decomposition to give the mercaptoamines occurred rapidly. The mercaptoamines were extracted with benzene and subsequently distilled under reduced pressure.

2 : 2′-Dimercaptodiethylamine (I) was first obtained as a by-product in the preparation of (IV) : a lower boiling fraction was always obtained in the final distillation, and was identified as (I) by iodine titration and analysis of the free base and its hydrochloride. Evidently it arose from the presence of diethanolamine in the commercial grade of triethanolamine used for the preparation of trichlorotriethylamine. It was observed that the hydrochloride of this amine, obtained from commercial triethanolamine and thionyl chloride, was impure since it had m. p. 112—120°, whereas the pure hydrochloride has m. p. 130—131° (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914). The impurity was clearly 2 : 2′-dichlorodiethylamine hydrochloride, which subsequently reacted with the thiourea giving diethylamine-2 : 2′-bis*iso*thiouronium trihydrochloride, which gave the dimercaptoamine on decomposition with alkali. However, all attempts to prepare a crystalline thiouronium salt from pure 2 : 2′-dichlorodiethylamine hydrochloride and thiourea in boiling alcohol were unsuccessful. It was found that the dithiol could be prepared, though in very poor yield, by boiling 2 : 2′-dichlorodiethylamine hydrochloride with

two mols. of thiourea in alcoholic solution, removing the solvent, and treating the residual syrup with aqueous alkali. A small quantity of the dithiol was obtaining by extracting the aqueous solution with benzene.

It seems probable that the anomalous behaviour of 2 : 2′-dichlorodiethylamine hydrochloride towards thiourea is due to its rapid decomposition in boiling alcoholic solution: similar anomalies were observed in its reaction with potassium thiocyanate under the same conditions (see below). It is interesting to note, however, that the yields of the dithiol obtained as described above, from crude 2 : 2′ : 2″-trichlorotriethylamine containing the dichloroamine, are fairly satisfactory, and it is possible that the decomposition of the secondary amine is inhibited by the presence of a larger amount of the tertiary amine.

The mercaptoamines were characterised as their *hydrochlorides* and by conversion into the corresponding benzoates which formed well-crystallised *hydrochlorides*. The latter were prepared by shaking the mercaptoamines with 10% aqueous alkali and benzoyl chloride, extracting the oily benzoyl derivatives with ether, and passing dry hydrogen chloride into the ethereal solution. The dithiol (I), which might have been expected to give a non-basic *NSS′*-tribenzoyl derivative, failed to give a crystalline product with benzoyl chloride and with *o*-nitrobenzoyl chloride.

All four mercaptoamines were colourless oils of very peculiar odour, miscible with ether and benzene, but only rather sparingly soluble in water. On exposure to air, rapid oxidation occurred, giving viscous gums, presumably chain-polymeric disulphides. The normal reactions of both thiols and amines were shown, the compounds being soluble in aqueous acids and strong alkalis. Well-defined salts were formed with mineral acids, and the thiol groups could be titrated quantitatively with iodine solution. Reaction occurred readily with acrylonitrile (cf. Albertson and Clinton, *loc. cit.*) and with dichloroarsines and arsine oxides of the types $RAsCl_2$ and RAsO, giving compounds which will be described in succeeding papers. Complexes were readily formed with a large number of metal ions, those formed with nickel being particularly noteworthy (see Part III, to be published).

Another possible method of obtaining the mercaptoamines was investigated: this consisted in reduction of the corresponding thiocyanates prepared from the chloroamines and potassium thiocyanate. Methyl-2 : 2′-dichlorodiethylamine, 2 : 2′-dichlorotriethylamine, and 2 : 2′ : 2″-trichlorotriethylamine all reacted readily with potassium thiocyanate in boiling alcohol to give oily thiocyanates, which formed well-crystallised hydrochlorides. *Methyl-2 : 2′-dithiocyanodiethylamine hydrochloride*, *2 : 2′-dithiocyanotriethylamine hydrochloride*, and *2 : 2′ : 2″-trithiocyanotriethylamine hydrochloride* all formed white prisms from alcohol–ether, readily soluble in water. On addition of alkali, the oily free bases were precipitated. Reduction of these compounds with zinc and dilute sulphuric acid apparently yielded a small amount of the corresponding mercaptoamines, but isolation was too difficult and the yield too poor for the method to be of any preparative value. 2 : 2′-Dithiocyanodiethylamine could not be obtained from 2 : 2′-dichlorodiethylamine or its hydrochloride by reaction with potassium thiocyanate; a complex mixture of products was formed and was not investigated further.

In the preparation of methyl-2 : 2′-dithiocyanodiethylamine hydrochloride, another compound was isolated in small yield. This was shown to be an ionic thiocyanate by its reaction with ferric chloride and analysis indicated that it was *NN′-dimethyldi-2-chloroethylpiperazinium dithiocyanate*. This was undoubtedly formed by dimerisation of the chloroamine, and the piperazinium structure was confirmed by the fact that acetylene was evolved when it was boiled with concentrated alcoholic potash.

Experimental.

Methyldi-(2-isothioureido-S-ethyl)amine Trihydrochloride.—Methyl-2 : 2′-dichlorodiethylamine hydrochloride (Eisleb, *Ber.*, 1941, **74**, 1433, 96 g.) and thiourea (80 g.) in alcohol (400 c.c.) were refluxed for 3 hours. The resulting solution was cooled in ice; some of the product then separated in a sticky condition. Dry hydrogen chloride was passed in with stirring and cooling in ice. More of the product separated, and had become completely solid at 0° overnight. It was filtered off, washed with acetone, and dried. A portion was twice recrystallised from alcohol containing a little water. The *compound* had m. p. 200° (decomp.) (Found: C, 25·7; H, 6·0; N, 20·2. $C_7H_{20}N_6Cl_3S_2$ requires C, 25·4; H, 5·8; N, 20·3%). Yield of crude product, 140 g. (80%).

Methyl-2 : 2′-dimercaptodiethylamine (III).—To a solution of the above crude trihydrochloride (103 g.) in water (200 c.c.), 20% sodium hydroxide solution (180 c.c.) was added. The solution was rapidly heated to 95° and then cooled. The dithiol, some of which had separated as an oil, was extracted with benzene (3 × 100 c.c.). The benzene solution was dried (Na_2SO_4), the solvent removed, and the residue distilled under reduced pressure. The *dithiol* (27·5 g.; 61%) was obtained as a clear colourless liquid, b. p. 105—107°/11 mm. (Found: C, 40·0; H, 8·8; N, 8·9. $C_5H_{13}NS_2$ requires C, 39·7; H, 8·6; N, 9·3%). Titration with 0·1N-iodine indicated a purity of 97%. The *hydrochloride*, white needles,

very hygroscopic, prepared in ether and recrystallised from alcohol-ether, had m. p. 104° (Found: C, 31·6; H, 7·8. $C_5H_{14}NClS_2$ requires C, 32·0; H, 7·5%).

A small portion of the dithiol was shaken with 10% aqueous sodium hydroxide and benzoyl chloride, and the oily product was dissolved in benzene. Dry hydrogen chloride was passed into the benzene solution; the *dibenzoate hydrochloride* was then precipitated as needles, m. p. 135° (from alcohol–ether) (Found: C, 55·5; H, 5·6. $C_{19}H_{22}O_2N_2ClS_2$ requires C, 55·9; H, 5·4%).

Ethyldi-(2-isothioureido-S-ethyl)amine.—2 : 2′-Dichlorotriethylamine (Ward, *loc. cit.*) (170 g.) and thiourea (152 g.) in alcohol (600 c.c.) were refluxed for 3 hours. After cooling, dry hydrogen chloride was passed into the mixture with stirring and cooling in ice. The *trihydrochloride* (335 g.) which had separated was filtered off and washed with acetone. A portion, recrystallised from alcohol containing a little water, formed white needles, m. p. 238—239° (decomp.) (Found, after drying at 100°: C, 26·6; H, 6·4; N, 19·8. $C_8H_{22}N_6Cl_3S_2$ requires C, 26·8; H, 6·2; N, 19·5%).

2 : 2′-*Dimercaptotriethylamine* (II).—To a solution of the trihydrochloride (300 g.) in water (400 c.c.), 20% sodium hydroxide solution (500 c.c.) was added. After being heated to 95° for a few minutes the solution was cooled, and the mercapto-amine, some of which had separated as an oil, was extracted with benzene (3 × 250 c.c.). The extract was dried (Na_2SO_4), the solvent removed, and the residue distilled under reduced pressure. The *dithiol* (75 g.; 55%) was obtained as a colourless liquid, b. p. 108—109°/4 mm. (Found: C, 36·5; H, 7·5; N, 7·3. $C_6H_{15}NS_2$ requires C, 36·5; H, 7·5; N, 7·1%). The *hydrochloride* formed hygroscopic white needles from alcohol–ether, m. p. 97—99° (Found: C, 36·1; H, 8·1. $C_6H_{16}NClS_2$ requires C, 35·7; H, 7·9%). The *dibenzoate hydrochloride*, prepared as for that of (III), formed needles from alcohol, m. p. 159° (Found: C, 58·7; H, 6·2. $C_{20}H_{24}O_2N_2ClS_2$ requires C, 58·8; H, 5·9%).

Tri-(2-isothioureido-S-ethyl)amine Tetrahydrochloride.—Pure 2 : 2′ : 2″-trichlorotriethylamine hydrochloride (Ward, *loc. cit.*) (m. p. 130°; 120 g.) and thiourea (115 g.) were refluxed in alcohol (400 c.c.) for 2 hours. On cooling, the *product* crystallised (203 g.; m. p. 216°). A small fraction was recrystallised from alcohol containing a little water and formed prisms, m. p. 219° (decomp.) (Found: Cl, 30·5; N, 20·3. $C_9H_{25}N_7Cl_4S_3$ requires Cl, 30·3; N, 20·9%).

2 : 2′ : 2″-*Trimercaptotriethylamine* (IV).—To a solution of the tetrahydrochloride above (156 g.) in water (200 c.c.), 20% sodium hydroxide solution (275 c.c.) was added. The solution was rapidly heated just to boiling; most of the trithiol then separated as an oil. After rapid cooling, the mixture was extracted with benzene (3 × 100 c.c.), the benzene solution was separated and dried (Na_2SO_4), and the solvent was removed. The residual oil was distilled under reduced pressure. The *trithiol* (30 g.; 45%) was obtained as a viscous oil, b. p. 145—147°/7 mm. (Found: C, 36·2; H, 8·0; N, 7·3. $C_6H_{15}NS_3$ requires C, 36·5; H, 7·5; N, 7·1%). The *hydrochloride*, prepared in ether and recrystallised from alcohol–ether, formed very hygroscopic white needles, m. p. 82—83° (Found: C, 30·9; H, 7·4. $C_6H_{16}NClS_3$ requires C, 30·8; H, 6·9%). The *tribenzoate hydrochloride*, prepared as for (III), formed needles from alcohol, m. p. 131° (Found: C, 59·9; H, 5·4. $C_{27}H_{28}O_3NClS_3$ requires C, 59·4; H, 5·2%).

2 : 2′-*Dimercaptodiethylamine* (I).—The crude product obtained from thionyl chloride and commercial triethanolamine (m. p. 112—120°; 120 g.) and thiourea (115 g.) were refluxed in alcohol (400 c.c.) for 2 hours. The solvent was distilled off, and the semi-solid residue dissolved in water (200 c.c.). 20% Sodium hydroxide solution (270 c.c.) was then added and the mixture heated to boiling. After rapid cooling, the mixture was extracted with benzene (5 × 100 c.c.), the benzene solution separated, dried (Na_2SO_4), and the solvent removed. The residual oil was distilled under reduced pressure and the main fraction (42 g.; b. p. 100—150°/7 mm.) was collected and then redistilled using a 12 cm. column. Two fractions were obtained: the *dithiol*, b. p. 100—105°/7 mm. (12 g.) (Found: C, 35·1; H, 8·0; N, 10·2. $C_4H_{11}NS_2$ requires C, 35·0; H, 8·0; N, 10·2%), and the trithiol (IV), b. p. 144—147°/7 mm. (24 g.). The *hydrochloride* of the dithiol formed hygroscopic white plates, m. p. 161° (from alcohol–ether) (Found: C, 27·9; H, 7·2. $C_4H_{12}NClS_2$ requires C, 27·6; H, 6·9%).

Methyl-2 : 2′-dithiocyanodiethylamine Hydrochloride.—Methyl-2 : 2′-dichlorodiethylamine (5·2 g.) was added to a solution of potassium thiocyanate (7 g.) in water (100 c.c.) and alcohol (50 c.c.). The mixture was boiled for 0·5 hour, water added, and the alcohol distilled off; the product then separated as an oil, which was dissolved in benzene. The benzene solution was dried, and dry hydrogen chloride passed in. The *hydrochloride* which separated was recrystallised from alcohol–ether; m. p. 121—122° (Found: N, 17·4. $C_7H_{12}N_3ClS_2$ requires N, 17·7%). Partial evaporation of the mother liquor after benzene extraction gave a compound which separated in small plates, m. p. 192° (decomp.). This gave a red colour with ferric chloride solution, indicating it to be an ionic thiocyanate, and, on boiling with 20% alcoholic potash, acetylene was evolved, indicating that the substance was probably a piperazinium diquaternary salt, *i.e.*, NN′-*dimethyldi-2-chloroethylpiperazinium dithiocyanate* (Found: N, 15·3; Cl, 20·0. $C_{12}H_{22}N_4Cl_2S_2$ requires N, 15·7; Cl, 19·8%).

2 : 2-*Dithiocyanotriethylamine Hydrochloride.*—Prepared exactly as above, from 2 : 2′-dichlorotriethylamine (5·5 g.) and potassium thiocyanate (7 g.), this *salt* formed white needles (from alcohol), m. p. 113—114° (Found: N, 16·8. $C_8H_{14}N_3ClS_2$ requires N, 16·7%).

2 : 2′ : 2″-*Trithiocyanotriethylamine Hydrochloride.*—Prepared exactly as above, from 2 : 2′ : 2″-trichlorotriethylamine (4 g.) and potassium thiocyanate (6 g.), this *salt* formed white needles (from alcohol), m. p. 153—155° (Found: N, 17·8. $C_9H_{13}N_4ClS_2$ requires N, 18·1%).

The greater part of this work was done in No. 2 Anti-Gas Laboratory, R.E., during 1944, and it was completed at the Chemical Defence Experimental Station, Porton, Wilts.

We are indebted to the Director General of Scientific Research (Defence), Ministry of Supply, and to the War Office, for permission to publish these results, and to Mr. J. H. R. Slade for much experimental assistance.

Micro-analyses were performed by Mr. G. Ingram.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 29th,* 1946.]

61. *Studies in the Thiazole Series. Part I. The Reaction between Thiourea and s-Dichloroacetone.*

By JOHN HARLEY-MASON.

The reaction between two molecules of thiourea and one molecule of *s*-dichloroacetone gives rise to two products according to the temperature of reaction. In boiling methyl alcoholic solution, 2-*amino*-4-*thiazolylmethyl*iso*thiourea dihydrochloride* (I) is formed, whereas by reaction without a solvent at *ca.* 220° the product is 2 : 2′-*diamino*-4 : 4′-spiro*thiazoline dihydrochloride* (II). At intermediate temperatures, mixtures of these products are obtained. Treatment of (I) with alkali leads to the normal *iso*thiourea dismutation, giving 2-*amino*-4-*mercaptomethylthiazole* (III).

THE reaction between thiourea and aldehydes and ketones halogenated in the α-position is well known, 2-aminothiazoles being obtained. There appears to be no record, however, of the condensation of thiourea with an αγ-dihalogenated ketone,* and accordingly the reaction between thiourea and *s*-dichloroacetone was studied.

The reaction was first examined in ethyl alcoholic solution. When an ethyl alcoholic solution of two molecular proportions of thiourea and one of dichloroacetone was heated gently, an exothermic reaction began when the temperature reached 50°. The mixture boiled spontaneously, the reaction being apparently complete in a few mixtures. On cooling, a large amount of white crystalline material separated. This material (*A*) decomposed without melting above 250°, was readily soluble in water, and analysis of a recrystallised sample indicated the empirical formula $C_5H_{10}N_4Cl_2S_2$, showing that it was formed from two molecules of thiourea and one molecule of dichloroacetone with the elimination of one molecule of water. On treatment with aqueous alkali and warming, decomposition occurred, giving an oil which contained a free thiol group, and dicyanodiamide. Evidently, therefore, this decomposition represented the normal dismutation of an *iso*thiourea (cf. *e.g.*, Arndt, *Ber.*, 1921, **54**, 2236). The substance (*A*) was therefore regarded as 2-*amino*-4-*thiazolylmethyl*iso*thiourea dihydrochloride* (I) and the thiol as 2-*amino*-4-*mercaptomethylthiazole* (III). The compound (III), which could be purified by high-vacuum distillation, formed a thick oil which failed to crystallise. It was characterised by oxidation to the corresponding *disulphide* (IV), which was a solid, and by the formation of a *diacetyl* and a *dibenzoyl* derivative.

It was observed that the comparatively violent reaction which took place between thiourea and dichloroacetone in very concentrated alcoholic solution gave a by-product on performing the alkaline dismutation of the product. This separated from the aqueous solution in small plates, m. p. 192—194° (decomp.) (*B*), was a diacid base, and formed a dihydrochloride (decomp. without melting above 250°) analysis of which indicated the same formula as (I). It was, however, not identical with (I), since on treatment with alkali it merely regenerated the base (*B*), which was stable to alkali. It appeared, therefore, that the dihydrochloride of (*B*) was formed as a by-product when the reaction was allowed to become violent so that local over-heating occurred. Accordingly, the reaction at temperatures higher than that of boiling ethyl alcohol was investigated.

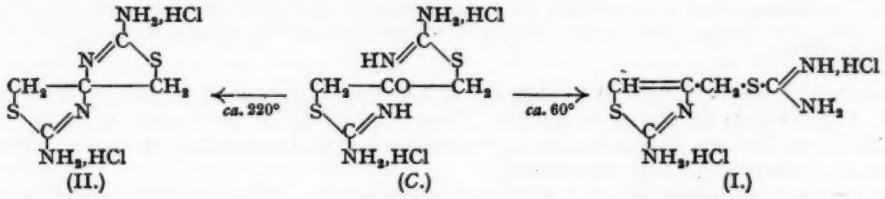
When an intimate mixture of the two components was heated gently, reaction set in at about 60° and became very violent, the temperature rising to about 220°, with formation of a hard mass. On dissolving this in water, boiling with charcoal to remove dark impurities, and basifying the filtrate, an excellent yield of the base (*B*) was obtained. There was no indication of the formation of (I). The base was very sparingly soluble in most organic solvents, but could be recrystallised from water. It was a rather stable substance, being unchanged by boiling acid and by short boiling with 10% sodium hydroxide solution. Longer boiling with the latter reagent caused slow decomposition with darkening and evolution of ammonia, but no definite product could be identified. A *dihydrochloride* (II) and a *dipicrate* were readily obtained. It was regarded as 2 : 2′-*diamino*-4 : 4′-spiro*thiazoline* (V), isomeric with the free base corresponding to (I).

Evidently the reaction could proceed in either of two directions according to the temperature, and it was found that, by working in methyl alcoholic solution, (I) could be obtained free from

* *Note added in Proof.*—Since this paper was submitted for publication, work on the reaction between thiourea and *s*-dichloroacetone has been described by Sprague, Land, and Ziegler (*J. Amer. Chem. Soc.*, 1946, **68**, 2155). These authors prepared the compound (I) by reaction of the two components in ethyl alcoholic solution, and from it the disulphide (IV) by a method similar to that described above. They did not, however, examine the reaction at higher temperatures and consequently did not obtain the spirocyclic compound (V).

(II), while on the other hand, by working without a solvent at a much higher temperature, (II) could be obtained free from (I). At intermediate temperatures, mixtures were obtained, *e.g.*, in 2-ethoxyethyl alcohol (b. p. 135°) a mixture containing approximately 60% of (I) and 40% of (II) was obtained. In ethyl alcohol, (I) alone was formed if the solution was relatively dilute, but in concentrated solution, when local overheating may have occurred due to the violence of the reaction, a small amount of (II) was formed.

The reaction may be represented as under, elimination of water from the hypothetical intermediate (*C*) occurring in either of two directions.



It was of interest to know whether the reaction paths were independent, or whether (I) was always first formed, and converted into (II) at higher temperatures, Both (I) and (II) decomposed completely without melting above 250°, without showing any signs of previous interconversion. (I) was recovered completely unchanged after 12 hours' boiling in 2-ethoxyethyl alcohol containing a little water. The free base (V) decomposed completely at its melting point, while the free base from (I), prepared by basifying an ice-cold concentrated solution with the calculated amount of alkali, decomposed very readily even at room temperature to give (III), and no sign of isomerisation could be detected. It seems therefore that the two reaction paths are quite independent.

An attempt was made to prepare a bissulphanilyl derivative of the disulphide (IV), by treatment with *p*-acetamidobenzenesulphonyl chloride in pyridine. No crystalline product could, however, be isolated and it appeared that the sulphonyl chloride had attacked the disulphide linkage. Attempts to cause the spirocyclic base to react with the same reagent were also unsuccessful. The disulphide was, however, readily converted into a *diacetyl* derivative by acetic anhydride.

Resolution of the racemic *spiro*-compound (II) was not attempted.

Experimental.

2-Amino-4-thiazolylmethylisothiourea Dihydrochloride (I).—Finely powdered thiourea (31 g.) and *s*-dichloroacetone (25 g.) were added to methyl alcohol (200 c.c.). The mixture was heated under reflux on the water-bath. A vigorous reaction set in, and subsided in about 5 minutes. Heating was continued for a further 10 minutes. On cooling, the *product* (47 g., 90%) separated as a white crystalline mass. A small portion was recrystallised from alcohol containing a little water and formed prisms, which decomposed without melting above 250° (Found: C, 22·5; H, 4·0; N, 21·2. $C_5H_8N_4S_2,2HCl$ requires C, 22·9; H, 3·8; N, 21·5%).

The dihydrochloride (2·6 g.) was dissolved in water (6 c.c.) and 10% sodium hydroxide solution (8 c.c.) added with ice-cooling and stirring. The *base* which separated in small white plates was rapidly filtered off, washed with a little water, and dried in a vacuum desiccator; m. p. 106° (decomp.) (on rapid heating) (Found: N, 29·6. $C_5H_8N_4S_2$ requires N, 29·8%). The compound was unstable and soon decomposed on standing even at room temperature, acquiring a " mercaptan " odour.

2-Amino-4-mercaptomethylthiazole (III).—2-Amino-4-thiazolylmethylisothiourea dihydrochloride (52 g.) was dissolved in water (150 c.c.), and a solution of sodium hydroxide (16 g.) in water (80 c.c.) was added. The mixture was rapidly heated to 100°, kept at this temperature for 2 minutes, and rapidly cooled; some of the product then separated as an oil. Sodium hydrosulphite (3 g.) was added to prevent oxidation of the thiol, and the mixture was extracted with ether (3 × 100 c.c.). The ethereal solution was dried (Na_2SO_4), the ether removed, and the residual pale yellow oil distilled in a vacuum in a current of hydrogen. The *product* formed a very viscous oil, b. p. 135—140°/2 mm., which failed to crystallise. Yield, 15 g. (51%) (Found: C, 32·4; H, 4·0; N, 19·1. $C_4H_6N_2S_2$ requires C, 32·8; H, 4·1; N, 19·2%). Concentration of the aqueous solution yielded dicyanodiamide (m. p. and mixed m. p. 205°). A portion of the thiol was shaken with benzoyl chloride and aqueous sodium hydroxide, yielding the *dibenzoyl* derivative, needles (from alcohol), m. p. 147—148° (Found: N, 7·8. $C_{18}H_{14}O_2N_2S_2$ requires N, 7·9%). Another portion was boiled with acetic anhydride and acetic acid, and poured into water to precipitate the *diacetyl* derivative; white felted needles (from dilute alcohol), m. p. 145—147° (Found: N, 12·4. $C_8H_{10}O_2N_2S_2$ requires N, 12·2%).

Bis-(2-amino-4-thiazolylmethyl) Disulphide (IV).—2-Amino-4-mercaptomethylthiazole (3 g.) was dissolved in 2N-hydrochloric acid (10 c.c.) and 3% hydrogen peroxide (12 c.c.) was added. After 1 hour at room temperature, the *disulphide* was precipitated by the addition of ammonia and recrystallised from alcohol (sparingly soluble); it formed prisms, m. p. 168° (Found: N, 19·5. $C_8H_{10}N_4S_4$ requires N, 19·3%). A portion was acetylated by boiling with acetic anhydride and acetic acid, and poured into

water; the *diacetyl* derivative separated and was recrystallised from 2-ethoxyethyl alcohol, from which it separated in prisms, m. p. 227—228° (Found: N, 14·4. $C_{12}H_{14}O_2N_4S_2$ requires N, 14·8%).

2 : 2′-*Diamino*-4 : 4′-spiro*thiazoline* (V).—An intimate mixture of thiourea (16 g.) and dichloroacetone (12·5 g.) was placed in a 200 c.c. bolt-head flask and heated cautiously on the water-bath. When the temperature of the mixture reached *ca.* 60°, a violent reaction began, and the flask was at once removed from the water-bath. The temperature rose rapidly to *ca.* 220° and the mixture, which had at first liquefied, set to a hard solid mass and some darkening occurred. When cold, the mass was chipped out, ground, and extracted with boiling alcohol (100 c.c.) to remove soluble impurities. The residue was dissolved in water (100 c.c.), boiled with charcoal, and ammonia added to the hot filtrate. The product was precipitated in crystalline form, and after cooling was collected and washed. Recrystallised from water (rather sparingly soluble) it formed prisms, m. p. 192—194° (decomp.) (Found: C, 32·2; H, 4·6; N, 30·1. $C_5H_8N_4S_2$ requires C, 31·9; H, 4·3; N, 29·8%). Yield, 14·5 g. (78%). Treatment with hydrochloric acid gave the *dihydrochloride* (prisms) which was recrystallised by dissolving it in a small amount of hot water and adding concentrated hydrochloric acid until separation began; it decomposed without melting above 250° (Found: Cl, 27·5. $C_5H_8N_4S_2,2HCl$ requires Cl, 27·1%). The *dipicrate* formed yellow prisms from hot water, m. p. 210—212° (decomp.) (Found: N, 15·3. $C_5H_8N_4S_2,2C_6H_3O_7N_3$ requires N, 15·1%).

Reaction in 2-Ethoxyethyl Alcohol.—Finely powdered thiourea (50 g.) and dichloroacetone (40 g.) were added to 2-ethoxyethyl alcohol (200 c.c.), and the mixture was heated over a free flame under reflux until reaction set in; the flame was then at once removed. As the reaction proceeded, the mixture boiled and some of the product began to separate. After cooling, the product was filtered off. Yield, 75 g. of mixed hydrochlorides.

The mixed hydrochlorides (52 g.) were dissolved in water (150 c.c.) and to the boiling solution a concentrated solution of sodium hydroxide (16 g.) was added. Some of the spirocyclic base separated at once and was filtered off hot. The filtrate was cooled, treated with sodium hydrosulphite (3 g.), and extracted with ether (3 × 100 c.c.). Some more of the spirocyclic base separated during the extraction and was filtered off. Total yield, 15·1 g. The ethereal solution was worked up for the thiol as above. Yield, 13·4 g.

The greater part of this work was done in No. 2 Anti-Gas Laboratory R.E. during 1944, and it was completed at the Chemical Defence Experimental Station, Porton, Wilts.

I am indebted to the Director General of Scientific Research (Defence), Ministry of Supply, and to the War Office, for permission to publish these results, and to Mr. J. H. R. Slade for much experimental assistance. Micro-analyses were performed by Mr. G. Ingram.

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62. *A General Method for the Preparation of Solid Aryldiazonium Sulphates.*

By HERBERT H. HODGSON and A. P. MAHADEVAN.

The general diazotisation procedure of Hodgson and Walker (*J.*, 1933, 1620), or the inverted variation of it for amines which are sparingly soluble in glacial acetic acid (Hodgson and Turner, *J.*, 1943, 86), is applicable to all amines capable of diazotisation, and solid diazonium sulphates are precipitated from their solutions by addition of ether, or other suitable solvent, in solid crystalline condition. This process has been applied to α-naphthylamine, *m*-toluidine, and *m*-anisidine, hitherto reported as not diazotised but nitrosated by nitrosylsulphuric acid.

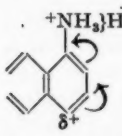
KNOEVENAGEL'S generalised method (*Ber.*, 1890, **23**, 2995) for obtaining solid diazonium salts by suspending the dry amine salt in ethyl alcohol and treating it with an alkyl nitrite (originally employed by Schmitt, *Ber.*, 1868, **1**, 67, for obtaining the diazonium chlorides of the aminophenols; cf. also Meyer and Stuber, *Annalen*, 1873, **165**, 187; Cameron, *Amer. Chem. J.*, 1898, **20**, 229) is valuable as a laboratory means for diazotising amines which are not easily dealt with by the direct method (cf. Kaufler, *Z. Farb.-Ind.*, 1903, **2**, 469) but is stated (Saunders "The Aromatic Diazo-compounds and their Technical Applications", Edward Arnold & Co., London, 1936, p. 15) to be unlikely to compel an amine of low reactivity to yield its diazo-derivative; *e.g.*, only monodiazotisation results with 2 : 7-naphthylenediamine (Kaufler and Karrer, *Ber.*, 1907, **40**, 3263). Hantzsch and Jochem (*Ber.*, 1901, **34**, 3337) found it better to use glacial acetic acid in place of alcohol (cf. also Schoutissen, *Rec. Trav. chim.*, 1921, **40**, 763, who carries out the operation more expeditiously by dissolving the amine in alcohol and preparing the salt immediately before adding the alkyl nitrite). The molecule of water produced in the reaction causes some difficulty, since ether is generally used to precipitate the diazonium salts from hydroxylic solvents, and the salts are prone to be sticky if a solvent should be employed in which the reaction water is not miscible; consequently, attempts have been made (S.C.I., D.R.-P. 575,832; F.P. 727,293; Sw.P. 152,611) to use non-hydroxylic solvents, *e.g.*, carbon tetrachloride, acetic ester, or benzene, and to bind the water produced in

the reaction by adding a desiccating agent such as calcined sodium sulphate. The diazonium sulphates are the most satisfactory for general use on account of their stability, some, such as *p*-nitrobenzenediazonium and dianisidinetetrazonium sulphates, having been in commerce for years with no other stabiliser than free mineral acid, and considerable additions have recently been made to this class since easily isolated stable diazonium salts are attractive because the cost of stabilisers is saved, the solubility is good, and there is minimum of complication. Further, many aryldiazonium sulphates formerly thought to be dangerously unstable have been prepared by diazotisation in *ca.* 85% sulphuric acid with nitrosylsulphuric acid and precipitated therefrom by organic liquids miscible with the acid such as the lower aliphatic alcohols at temperatures well below 0°. Among the amines claimed (I.G., E.P. 441,085; Anm., I. 47,579; F.P.P. 776,009, 775,963; Sw.P. 177,263; D.R.-P. 622,306) as being suitable for this process are the nitroanilines, and the mono-, di-, and poly-halogenoaminophenol ethers. In this connection, Hantzsch and Borghaus (*Ber.*, 1897, **30**, 93) have shown that the solid tetrazosulphate is much more stable than the chloride in the case of both *m*- and *p*-tetrazobenzene. In the various processes referred to above, diazotisation can be brought about not only with alkyl nitrites in such solvents as those mentioned, but also with liquid nitrogen trioxide (cf. Bamberger, *Ber.*, 1894, **27**, 1948; Morgan and Upton, *J.*, 1917, **111**, 187), nitrosyl chloride, or nitrosylsulphuric acid.

The importance of the solid aryldiazonium sulphates may thus be realised from the variety of methods devised to obtain them, and of these the most general is that involving the use of nitrosylsulphuric acid. This method, however, fails when diazo-oxide formation occurs, as in the cases of the 2-nitro-1- and 1-nitro-2-naphthylamines, 2 : 4-dinitro-1-naphthylamine, 2 : 4-dibromo-1-naphthylamine, and 1 : 4-dibromo-2-naphthylamine; or when nitrous acid attacks some other part of the molecule in preference to the amino-group to form nitroso-compounds, as in the cases of *m*-toluidine or *m*-anisidine (I.G., D.R.-P. 561,425) and α-naphthylamine (I.G., E.P. 355,970; D.R.-P. 519,729) (cf. also Blangey, *Helv. Chim. Acta*, 1938, **21**, 1579).

Since it was especially for those amines mentioned above as prone to form diazo-oxides that Hodgson and Walker's method (*loc. cit.*) was devised, it appeared of interest to examine its general utility for the preparation of solid diazonium sulphates. All amines known to admit of diazotisation may be diazotised smoothly by this sulphuric acid–glacial acetic acid procedure, or when the amine is not too soluble by an inverted variant of it (Hodgson and Turner, *loc. cit.*), and the solution of the diazonium sulphate, when treated with sufficient ether for the purpose, affords the solid compound in beautiful crystalline form which can be freed from acid by first washing with a mixture of ether and glacial acetic acid and finally with ether, or by the use of a solvent such as ethyl acetate, which is soluble in the glacial acetic–sulphuric acid mixture but in which the diazonium sulphate is insoluble. Should the precipitation of the salt be made too rapidly and an oily form result by reason of admixed solvent (which seldom occurs), solidification is brought about by washing the oily precipitate with a little ethanol or by keeping it ice-cold for a short time. The yields are of the order of 70—100%.

By this means 2-nitro-, 2 : 4-dinitro-, and 2 : 4-dibromo-1-naphthalene- and 1-nitro-2-naphthalene-diazonium sulphates have been obtained in solid crystalline form, and also the diazonium sulphates of α- and β-naphthylamines, *m*-toluidine, and *m*-anisidine. The last four amines were all diazotised smoothly and almost completely by Hodgson and Walker's procedure (*loc. cit.*), and, when the glacial acetic–sulphuric acid solutions were diluted with ice, the aqueous solutions of the diazonium salts were stable and available for use. It would appear, therefore, that the nitrosation instead of diazotisation which is stated to occur (*loc. cit.*) with nitrosylsulphuric acid in 85% sulphuric acid must be connected with the presence of water in this medium, the reaction of the nitrous acid at the *p*-carbon atom being then more rapid than at the positive diazonium ionic group. This reaction would appear to support Kenner's views (*Chem. and Ind.*, 1941, **60**, 443) that nitrous acid under these conditions is a nucleophilic (anionoid) reagent, since the electronic effect is to render the *p*-carbon atom positively charged (see inset), and the salt formation to protect the amine from attack. The non-diazotisation by pure nitrosylsulphuric acid of α-naphthylamine, *m*-toluidine, and *m*-anisidine is common to other aromatic amines, so that nitrosation can occur in those amines prone to it, whereas when glacial acetic acid is added, the nitrosylsulphuric acid affords free nitrous acid which can then effect the diazotisation.



Schoutissen's technique of diazotising amines by addition of phosphoric acid to their solutions in nitrosylsulphuric acid (*J. Amer. Chem. Soc.*, 1933, **55**, 4531) is of much less utility for the

isolation of the diazonium sulphates by ether addition, because of the very limited solubility of ether in the phosphoric–sulphuric acid mixture.

Since Hodgson and Walker's method is general for all amines hitherto found to be capable of diazotisation, it follows that the preparation of solid diazonium sulphates may now be accomplished in all cases by a single procedure, and since ether is soluble in the glacial acetic–sulphuric acid mixture which retains the water formed in the diazotisation, the resulting separations of solid diazonium sulphate are not sticky.

Experimental.

General Procedure.—A cold solution of the amine (1 g.) in glacial acetic acid (10 c.c.) is stirred into the required amount of sodium nitrite (*ca.* 1 g. in most cases) dissolved in sulphuric acid (5 c.c., *d* 1·84) at 0°, and the mixture kept until the diazotisation is complete (usually *ca.* 10 minutes, but 30 minutes should be ample). Although the mixture is normally kept at *ca.* 0° during the addition, yet working at room temperature has never shown any decreased yield. Ether (50 c.c., or as much as required) is stirred gradually into the mixture, and the solid diazonium sulphate separates and is filtered off, the mixed acid being removed with ether–glacial acetic acid and finally with ether.

Analysis.—To determine the yield, the precipitated, washed solid is dissolved immediately in water, and the solution (filtered if necessary) is stirred into the appropriate amount of an alkaline β-naphthol solution; the insoluble azo-dye which is precipitated is removed, washed free from β-naphthol with hot 2% aqueous sodium hydroxide, and from alkali by hot water, dried, and weighed.

Typical yields of solid diazonium sulphates (%, in parentheses) were as follows: Aniline (72), benzidine (98), *p*-nitroaniline (75), *m*-phenylenediamine (72·3), α-naphthylamine (67), β-naphthylamine (68), *m*-toluidine (73·3), *m*-anisidine (73·8).

Remarks.—Precipitation of diazonium sulphate was almost instantaneous with tetrazotised benzidine, very rapid with *m*-phenylenediamine, and rapid in the cases of the other diazotised amines mentioned except aniline, from whose solution the diazonium sulphate separated more gradually All the diazonium sulphates were fairly stable.

The authors thank the Madras Government for a Research Scholarship to one of them (A. P. M.), and Imperial Chemical Industries Ltd. (Dyestuffs Division) for gifts of chemicals.

The Technical College, Huddersfield. [*Received, June 27th,* 1946.]

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63. *Some Reactions and Derivatives of 6- and 7-Nitro-2-naphthylamines. Part I. Bromination, Halogeno-derivatives, and the Preparation of the New 7-Nitro-2-naphthol.*

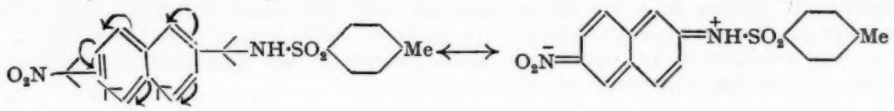
By Herbert H. Hodgson and Edward R. Ward.

The direct bromination of 6- and 7-nitro-2-naphthylamines and of their *p*-toluenesulphonyl derivatives takes place in the 1-position only, in contrast with the tribromination of β-naphthylamine in chloroform and its dibromination in pyridine solution. 6- and 7-Nitro-2-naphthylamines readily form mono- but only with difficulty di-toluene-*p*-sulphonamides. All the 2-halogeno-6- and -7-nitronaphthalenes and the 6- and 7-halogeno-2-naphthylamines have been prepared from a common source. The new 7-nitro-2-naphthol has been prepared, and the difference noted between decompositions of aqueous solutions of 6- and 7-nitronaphthalene-2-diazonium sulphates when dropped into boiling 20% sulphuric acid with production of naphthol, or, when boiled *in situ*, with resultant azo-compound formation.

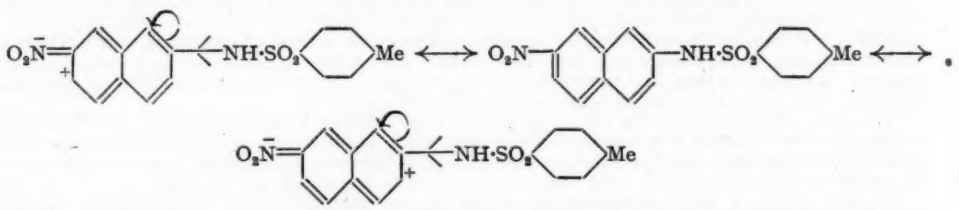
The direct bromination of 6- and 7-nitro-2-naphthylamines and of their toluene-*p*-sulphonyl derivatives occurred only in the 1-position whether in chloroform or pyridine solution, and a great excess of bromine had no further effect. This is in striking contrast with the bromination of β-naphthylamine, which Franzen and Stäuble (*J. pr. Chem.*, 1922, **103**, 352) found to take place successively in the order 1, 6, and 3, giving 1 : 3 : 6-tribromo-2-naphthylamine as the final product—a result similar to that in the bromination of β-naphthol, where 1 : 3 : 4 : 6-tetrabromo-2-naphthol is ultimately formed; also, Bell (*J.*, 1932, 2732) found that the bromination of toluene-*p*-sulphon-2-naphthalide in chloroform solution gave the 1 : 6-dibromo-derivative in analogy with its nitration (cf. Morgan and Micklethwait, *J.*, 1912, **101**, 148), but that in pyridine solution this naphthalide would not brominate further than the 1 : 3-derivative, although the toluene-*p*-sulphon-1 : 3 : 6-tribromo-2-naphthalide was formed in the chloroform solution of the 1 : 3-dibromo-compound, and toluene-*p*-sulphon-1 : 6-dibromo-2-naphthalide was readily converted into the 1 : 3 : 6-tribromo-compound in pyridine solution.

The unique monobromination of 6-nitro-2-naphthylamine and of its toluene-*p*-sulphonyl derivative must therefore be ascribed to the deactivation of the 3-position by the 6-nitro-group, which, by resonance with the amino- and toluene-*p*-sulphonamido-groups (cf. Robinson and

Thompson, *J.*, 1931, 2015, for ready transmission of effects between the 2- and the 6-position), causes the nitrogen to become kationoid (electrophilic) in the contributing 2 : 6-quinonoid structure of the resonance hybrid :



Similarly, in 7-nitro-2-naphthylamine and its toluene-*p*-sulphonyl derivative there is resonance into the 3 : 7-ionic quinonoid structure whereby the 3-position is deactivated :



In both cases activation is restricted to the 1-position of the contributing benzenoid structure of the resonance hybrid, and only monobromination takes place.

With a nitro-group in the 1-position, toluene-*p*-sulphon-1-nitro-2-naphthalide was shown to brominate readily in the 3-position in pyridine solution by Consden and Kenyon (*J.*, 1935, 1592), who explained this by salt formation of the sulphonamido-group with pyridine. A similar claim was made for toluene-*p*-sulphon-1 : 6-dinitro-2-naphthalide, although the fact of 3-bromination could not be definitely proved by them and their claim rests upon analogy. It is possible, however, that bromination could have occurred elsewhere, since the 6-nitro-group could restrain salt formation by pyridine at the toluene-*p*-sulphonamido-group as in the case of toluene-*p*-sulphon-6-nitro-2-naphthalide.

Earlier, Veselý and Dvorák (*Chem. Listy*, 1923, **17**, 163) had found that bromination of 4-, 5-, 6-, and 8-nitroaceto-2-naphthalides occurred exclusively in the 1-position; this can be readily explained as above.

On analogy with the effect of the nitro-group on halogenation, the similar electrophilic effect of the sulphonic acid group likewise directs and restricts halogenation to the 1-position; *e.g.*, aceto-2-naphthalide-6-sulphonic acid is chlorinated in the 1-position only (Steiger, G.P. 536,995; *Chem. Abstr.*, 1932, **26**, 2747), and the 5-, 6-, and 7-sulphonic acids of β-naphthylamine all brominate exclusively in the 1-position (Heller, Arnold, and Schmidt, *Z. angew. Chem.*, 1930, **43**, 1132).

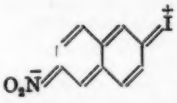
Proof of the constitution of 1-bromo-6-nitro-2-naphthylamine was given by deamination to the known 1-bromo-6-nitronaphthalene, and by conversion, *via* the Sandmeyer reaction, into the known 1 : 2-dibromo-6-nitronaphthalene (Hodgson and Turner, *J.*, 1943, 579). 1-*Bromo*-7-*nitro*-2-*naphthylamine* was orientated by conversion *via* the Sandmeyer reaction into 1 : 2-*dibromo*-7-*nitronaphthalene*, followed by reduction to 7 : 8-*dibromo*-2-*naphthylamine* by the iron-powder method of Hodgson and Marsden (*J.*, 1944, 398), and deamination to the known 1 : 2-dibromonaphthalene.

Toluene-p-*sulphon*-1-*bromo*-6- and -7-*nitro*-2-*naphthalides* were readily hydrolysed by concentrated sulphuric acid to the free amines and so orientated.

Probably as a result of easy resonance with consequent partial inhibition of the anionoid reactivity of the 2-amino-group, 6- and 7-nitro-2-naphthylamines, while forming mono-toluene-*p*-sulphonyl derivatives with ease, were converted only with difficulty into the di-derivatives, even when a large excess of toluene-*p*-sulphonyl chloride in pyridine was used, although the reaction proceeded a little more readily in water (cf. Hodgson and Turner, *J.*, 1943, 391; Hodgson and Hathway, *J.*, 1944, 538; 1945, 453). The further weakening of the anionoid reactivity above by the presence of bromine in the 1-position appears to prevent toluene-*p*-sulphonation altogether, and the toluene-*p*-sulphon-1-bromo-6- and -7-nitro-2-naphthalides had to be prepared by bromination of toluene-*p*-sulphon-6- and -7-nitro-2-naphthalides.

All the possible 2-halogeno-6- and -7-nitronaphthalenes have been prepared from a common source, and also 6- and 7-halogeno-2-naphthylamines; of these compounds only 2-bromo-6-nitronaphthalene and 6-bromo-2-naphthylamine have been prepared before.

2-*Iodo*-6-*nitronaphthalene* could not be reduced by the methyl alcoholic–alkaline sulphide procedure of Hodgson and Birtwell (*J.*, 1944, 75), the nitro-compound being recovered unchanged; this resistance to sulphide reduction may well be a result of facile resonance between the iodine and nitro-group (annexed), owing to the amphoteric character of the iodine, whereby the reactivity of the nitro-group is so decreased as to resist further acceptance of electrons from the reducing agent. In this respect the iodine is resonating like an amino-group; analogously, 6-nitro-2-naphthylamine also resists further reduction with alkaline sulphides, as do other nitronaphthylamines.



The new 7-*nitro*-2-*naphthol* as well as the known 6-nitro-2-naphthol have been readily obtained by decomposition of the corresponding 6- and 7-nitronaphthalene-2-diazonium sulphates when added to boiling 20% sulphuric acid (cf. Hodgson, E.P. 200,714). When solutions of the above diazonium sulphates were boiled *in situ*, almost quantitative yields were obtained of 6- and 7-*nitronaphthalene*-2 : 1′-*azo*-6′- and -7′-*nitro*-2′-*naphthols* (cf. the corresponding preparation of *m*-chlorophenol by the same device, and the complete conversion into azo-compound by heating *m*-chlorobenzenediazonium sulphate *in situ*).

6- and 7-Nitronaphthylamines form stable *anils* with *p*-nitrobenzaldehyde in glacial acetic acid solution.

Experimental.

Bromination of 6- *and* 7-*Nitro*-2-*naphthylamines.*—A solution of the requisite amine (1 g.) in dry chloroform (50 c.c.) was treated at 50° with 3 c.c. of a solution of bromine (1 c.c.) in dry chloroform (9 c.c.); the hydrobromide of 1-bromo-6-nitro- or 1-bromo-7-nitro-2-naphthylamine was then immediately precipitated, and was filtered off after cooling to room temperature. The hydrobromides could be basified by dilute ammonia or even by trituration with water, and the free bases were then crystallised from boiling glacial acetic acid or pyridine; yield of each, 1·25 g. (*ca.* 90%). Further small amounts were obtainable by concentrating the chloroform solutions.

1-Bromo-6-nitro-2-naphthylamine separated from pyridine in orange rods, m. p. 225—226° (Veselý and Dvorák, *loc. cit.*, give m. p. 222—223°) (Found: N, 7·4. Calc. for $C_{10}H_7O_2N_2Br$: N, 7·35%); the hydrochloride is stable only in hot concentrated hydrochloric acid and, like the hydrobromide, is hydrolysed by water. Deamination to 1-bromo-6-naphthalene was effected by adding a solution of the amine (2·5 g.) in sulphuric acid (5 c.c., *d* 1·84) to one of sodium nitrite (1 g.) in sulphuric acid (5 c.c., *d* 1·84), and then stirring the whole into glacial acetic acid (20 c.c.) below 20°; the mixture was kept for 30 minutes to complete the diazotisation and then stirred with red cuprous oxide (3 g.), added gradually over 15 minutes, during which time the temperature was allowed to rise to 40°; stirring was continued for a further 1 hour, after which the mixture was poured on ice and the precipitate containing 1-bromo-6-nitronaphthalene removed, washed in sequence with water, aqueous sodium carbonate, and water, and then extracted with ethanol (50 c.c.); on concentration of the extract 1-bromo-6-nitronaphthalene separated; it crystallised from aqueous pyridine in pale yellow micro-plates, m. p. and mixed m. p. with an authentic specimen prepared by Hodgson and Turner (*loc. cit.*) 130—131° (Found: N, 5·7. Calc. for $C_{10}H_6O_2NBr$: N, 5·5%). When 1-bromo-6-nitro-2-naphthylamine was diazotised as above and the solution added to one of cuprous bromide (5 g.) in hydrobromic acid (20 c.c., *d* 1·7), the mixture stirred for 3 hours, kept overnight, and then poured on ice, 1 : 2-dibromo-6-nitronaphthalene was precipitated; it crystallised from methanol–acetone in cream-coloured needles, m. p. 175° (Hodgson and Turner, *loc. cit.*, give m. p. 175°).

1-*Bromo*-7-*nitro*-2-*naphthylamine* crystallised from pyridine in orange-red rods which were redder and somewhat more soluble in organic solvents than the 6-nitro-isomeride above, and had m. p. 228° (Found: N, 10·6; Br, 30·0. $C_{10}H_7O_2N_2Br$ requires N, 10·4; Br, 30·0%). Diazotisation of the amine (2·5 g.) followed by treatment as above gave 1 : 2-*dibromo*-7-*nitronaphthalene* (2·9 g.) which crystallised from 80% pyridine in cream-coloured micro-needles, m. p. 147° (Found: N, 4·4. $C_{10}H_5O_2NBr_2$ requires N, 4·2%), which were very soluble in hot or cold pyridine and in ethylene chloride, soluble in chloroform, but only slightly soluble in cold ethanol.

7 : 8-*Dibromo*-2-*naphthylamine* was formed when finely powdered 1 : 2-dibromo-7-nitronaphthalene (2 g.) was refluxed for 3 hours with a mixture of iron powder (pin dust, 6 g.), ferrous sulphate (1 g.), and water (50 c.c.); the mixture was filtered cold, the solid washed with cold water, dried, and extracted with boiling ethanol, and the solvent removed from the crude 7 : 8-dibromo-2-naphthylamine which crystallised from 50% aqueous ethanol in scimitar-like clusters of colourless needles or from ethanol in similar clusters of colourless needles, m. p. 103—104° (Found: N, 4·8. $C_{10}H_7NBr_2$ requires N, 4·65%); the filtrate above yields only a very small additional amount when extracted by chloroform. On deamination as above, 1 : 2-dibromonaphthalene was obtained which crystallised from methanol in colourless needles, m. p. and mixed m. p. with authentic specimen 68° (Meldola and Streatfeild, *J.*, 1893, **63**, 1054, give m. p. 68°).

Action of Toluene-p-*sulphonyl Chloride on* 6- *and* 7-*Nitro*-2-*naphthylamines.*—The amine (2 g.) was ground with toluene-*p*-sulphonyl chloride (3 g.), added to pyridine (15 c.c.), the mixture heated on the water-bath for 2—3 hours with addition of a little sodium carbonate, then cooled and stirred into 10% hydrochloric acid; the precipitate of the sulphonamide was washed with water and extracted with 5% aqueous sodium hydroxide (500 c.c.), and the filtered extract cooled and neutralised with dilute hydrochloric acid; the precipitated monosulphonamide was then filtered off, washed with water, dried at 100°, and crystallised from glacial acetic acid. The alkali-insoluble residue of the sulphonamide was washed with water and crystallised from acetone. Only a very small yield of the disulphonamide was

obtained, and this was not appreciably increased even when a five-fold excess of toluene-*p*-sulphonyl chloride was used. With water instead of pyridine, and several equivalents of toluene-*p*-sulphonyl chloride, the yield of disulphonamide was somewhat improved.

Toluene-p-*sulphon*-6-*nitro*-2-*naphthalide* crystallised from ethanol in star-like clusters of colourless needles, m. p. 192° (Found: N, 8·4. $C_{17}H_{14}O_4N_2S$ requires N, 8·5%). *Bistoluene*-p-*sulphonyl*-6-*nitro*-2-*naphthylamine* crystallised from acetone or 50% aqueous acetone in colourless needles, m. p. 249° (Found: N, 5·8. $C_{24}H_{20}O_6N_2S_2$ requires N, 5·65%), which were readily soluble in ethanol.

Toluene-p-*sulphon*-7-*nitro*-2-*naphthalide* crystallised from ethanol in colourless needles, m. p. 176° (Found: N, 8·8. $C_{17}H_{14}O_4N_2S$ requires N, 8·55%); the sodium salt was only sparingly soluble in hot 5% aqueous sodium hydroxide and crystallised readily from the hot solution on cooling. *Bistoluene*-p-*sulphonyl*-7-*nitro*-2-*naphthylamine* crystallised from acetone in colourless needles, m. p. 231° (Found: N, 5·8. $C_{24}H_{20}O_6N_2S_2$ requires N, 5·65%).

Bromination of Toluene-p-*sulphon*-6- *and* -7-*nitro*2-*naphthalides*.—The naphthalide (1 g.) was dissolved in hot pyridine (10 c.c.) and the cold solution stirred with 1 c.c. of a solution of bromine (1 c.c.) in pyridine (9 c.c.); after 12 hours the mixture was stirred into 10% hydrochloric acid and the precipitate was removed, washed with water, dried, and crystallised from hot acetone or hot glacial acetic acid. No further bromination could be effected even with a great excess of the bromine solution.

Toluene-p-*sulphon*-1-*bromo*-6-*nitro*-2-*naphthalide* crystallised from hot acetone in cream coloured prisms, m. p. and mixed m. p. with authentic specimen (Hodgson and Turner, *loc. cit.*) 197—198°, which were hydrolysed by dissolution in sulphuric acid (*d* 1·84) at 40°, and the free amine identified with the 1-bromo-6-nitro-2-naphthylamine prepared by direct bromination.

Toluene-p-*sulphon*-1-*bromo*-7-*nitro*-2-*naphthalide* crystallised from boiling acetic acid in light yellow needles, m. p. 171—172° (Found: N, 6·8. $C_{17}H_{13}O_4N_2Br$ requires N, 6·65%), which were moderately soluble in pyridine and readily hydrolysed by dissolution in sulphuric acid (*d* 1·84) at 40° to 1-bromo-7-nitro-2-naphthylamine. Attempts to prepare these naphthalides by treating solutions of the respective amines in pyridine with toluene-*p*-sulphonyl chloride were unsuccessful, the free amines being recovered unchanged.

Anil Formation.—6- or 7-Nitro-2-naphthylamine (0·5 g.) and *p*-nitrobenzaldehyde (0·3 g.) were separately dissolved in minimum amounts of glacial acetic acid, and the mixed solutions refluxed for 1 hour. On cooling the anil separated; it was removed, washed with pyridine, and crystallised from hot ethanol or pyridine. 6:4′-*Dinitrobenzylidene*-2-*naphthylamine* crystallised from pyridine in yellow micro-needles, m. p. 258° (Found: N, 13·4. $C_{17}H_{11}O_4N_3$ requires N, 13·1%). 7:4′-*Dinitrobenzylidene*-2-*naphthylamine* crystallised from pyridine in yellow micro-needles, m. p. 193° (Found: N, 13·3. $C_{17}H_{11}O_4N_3$ requires N, 13·1%).

Halogeno-derivatives from 6- *and* 7-*Nitro*-2-*naphthylamines*.—*General diazotisation procedure.* The amine (2·5 g.) was boiled with hydrochloric acid (5 c.c., *d* 1·18) and water (25 c.c.), the mixture rapidly chilled, and treated at 0° with a solution of sodium nitrite (1 g.) in water (3 c.c.).

2-*Chloro*-6-*nitronaphthalene* was obtained when the 6-nitro-2-naphthylamine, diazotised as above, was added to a solution of cuprous chloride (5 g.) in hydrochloric acid (50 c.c., *d* 1·18) at 60°; when the reaction had ceased, the mixture was filtered cold and the precipitate was washed, dried, and extracted with ethanol (150 c.c., charcoal); from the concentrated extract almost pure 2-chloro-6-nitronaphthalene separated on cooling and was further purified by sublimation at 180—190°/15 mm.; lemon-yellow needles, m. p. 170° (Found: N, 6·9. $C_{10}H_6O_2NCl$ requires N, 6·7%). 2-Bromo-6-nitronaphthalene was obtained similarly, but by the use of hydrobromic instead of hydrochloric acid; it sublimed in lemon-yellow needles, m. p. 190° (McLeish and Campbell, *J.*, 1937, 103, give m. p. 190°) (Found: N, 5·6. Calc. for $C_{10}H_6O_2NBr$: N, 5·5%). 2-*Iodo*-6-*nitronaphthalene* was obtained from the diazo-solution above when, after removal of excess of nitrous acid by urea, it was treated with a solution of potassium iodide (10 g.) in the minimum amount of water; the precipitate was filtered off, washed successively with water, aqueous sodium thiosulphate, and water, dried, extracted with boiling ethanol (400 c.c.), the extract concentrated, and the separated 2-iodo-6-nitronaphthalene (2·6 g.) purified by sublimation at 190—200°/15 mm. to give very pale yellow rods, m. p. 231° (Found: N, 5·0. $C_{10}H_6O_2NI$ requires N, 4·7%), which were only sparingly soluble in boiling ethanol.

The 7-nitro-analogues were prepared and purified in like manner. 2-*Chloro*-7-*nitronaphthalene* (2·1 g.) sublimed in pale yellow needles, m. p. 136° (Found: N, 7·0. $C_{10}H_6O_2NCl$ requires N, 6·7%). 2-*Bromo*-7-*nitronaphthalene* (2·2 g.) sublimed in very pale yellow needles, m. p. 147—148° (Found: N, 5·7. $C_{10}H_6O_2NBr$ requires N, 5·55%). 2-*Iodo*-7-*nitronaphthalene* (2·4 g.) sublimed in almost colourless needles, m. p. 122° (Found: N, 5·0. $C_{10}H_6O_2NI$ requires N, 4·7%).

Reduction of the 2-*Halogeno*-6- *and* -7-*nitronaphthalenes*.—The halogeno-nitro-compound (1 g.) was suspended in hot ethanol (60 c.c.) and treated gradually with a solution of sodium hyposulphite (3·5 g.) in water (16 c.c.). The mixture was refluxed for 1 hour and filtered cold to remove most of the inorganic matter, water was added to the filtrate to increase the volume three- to four-fold, and the precipitate which appeared was redissolved by heating and the solution filtered hot. The almost pure halogeno-amine separated on cooling, and recrystallised from 40% aqueous pyridine in silvery micro-plates which were readily soluble in cold pyridine or ethanol. Yields were almost quantitative.

6-*Chloro*-2-*naphthylamine* had m. p. 123° (Found: N, 8·1. $C_{10}H_8NCl$ requires N, 7·8%). 6-Bromo-2-naphthylamine had m. p. 127° (Franzen and Stäuble, *loc. cit.*, give m. p. 128°) (Found: N, 6·4. Calc. for $C_{10}H_8NBr$: N, 6·3%). 6-*Iodo*-2-*naphthylamine* had m. p. 138° (Found: N, 5·3. $C_{10}H_8NI$ requires N, 5·2%). 7-*Chloro*-2-*naphthylamine* had m. p. 118—119° (Found: N, 7·9%). 7-*Bromo*-2-*naphthylamine* had m. p. 130° (Found: N, 6·4%). 7-*Iodo*-2-*naphthylamine* had m. p. 116° (Found: N, 5·1%).

Preparation of 6- *and* 7-*Nitro*-2-*naphthols*.—6- or 7-Nitro-2-naphthylamine (2 g.) was stirred with sulphuric acid (1·5 c.c., *d* 1·84) and water 20 c.c., and the mixture heated, chilled to obtain the sulphate in fine suspension, and then diazotised at 0° with sodium nitrite (1 g.) dissolved in the minimum amount of water. The solution of the diazonium sulphate was then dropped gradually into boiling 20% sulphuric acid (50 c.c.). A small amount of tar then formed. After evolution of nitrogen had ceased, charcoal

(2 g.) was added, and the mixture boiled for 2 minutes and rapidly filtered hot; the filtrate was cooled to 0°, and the almost pure nitronaphthol (*ca.* 0·4 g.) was collected and recrystallised from boiling water.

6-Nitro-2-naphthol was obtained in felted yellow needles, m. p. 155° (Gaess, *J. pr. Chem.*, 1892, **45**, 616; **46**, 160, gives m. p. 156—158°) (Found: N, 7·5. Calc. for $C_{10}H_7O_3N$: N, 7·4%). *6-Nitro-2-naphthyl acetate* was formed when 6-nitro-2-naphthol (0·2 g.) was heated with acetic anhydride (1 c.c.) and glacial acetic acid (1 c.c.) for 10 minutes. The cooled mixture was treated with water; the precipitated acetate crystallised from hot glacial acetic acid in colourless micro-needles, m. p. 147° (Found: N, 6·3. $C_{12}H_9O_4N$ requires N, 6·1%).

7-Nitro-2-naphthol crystallised in felted yellow needles, m. p. 159° (Found: N, 7·6. $C_{10}H_7O_3N$ requires N, 7·4%), which sublimed readily, were soluble in ethanol and slightly soluble in cold water, and gave no colour with ferric chloride. *7-Nitro-2-naphthyl acetate*, prepared like the 6-nitro-isomeride, crystallised from hot glacial acetic acid in colourless needles, m. p. 124° (Found: N, 6·4. $C_{12}H_9O_4N$ requires N, 6·1%).

When either of the diazo-solutions above was freed from excess of nitrous acid by urea and then boiled, the main product was a nitronaphthaleneazonitronaphthol with only a small amount of admixed nitronaphthol; the azo-compound was filtered off, washed repeatedly with boiling water to remove the nitronaphthol, and crystallised from nitrobenzene. The yields were almost quantitative. *6-Nitronaphthalene-2 : 1′-azo-6′-nitro-2′-naphthol* formed red micro-needles, m. p. 296° (Found: N, 14·7. $C_{20}H_{12}O_5N_4$ requires N, 14·4%), which gave a magenta colour with sulphuric acid changing to a bluish-red and then to a brown precipitate on dilution. *7-Nitronaphthalene-2 : 1′-azo-7′-nitro-2′-naphthol* formed red micro-needles, m. p. 317° (decomp.) (Found: N, 14·6%), which gave a magenta colour with sulphuric acid changing to a bluish-red and then to a brown precipitate on dilution.

When 7-nitro-2-naphthylamine was boiled with 5% aqueous sodium hydroxide for 6 hours it was recovered unchanged, as also was its acetyl derivative, which resisted replacement of the acetamido-group by the hydroxyl group even with boiling 20% aqueous sodium hydroxide.

The authors are indebted to the Charles Brotherton Trust for a Research scholarship (to E. R. W.), to Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals, and to Mr. Frank Hobson for micro-analyses.

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64. *The Absorption Spectra of Organic Compounds containing Nitrogen. Part I. Derivatives of Hydantoin.*

By R. E. STUCKEY.

The absorption spectra of hydantoin and of 5 : 5′-dimethyl-, 1 : 5 : 5′-trimethyl-, and 3-methyl-hydantoin in acid and alkaline solution are given. Evidence from this source indicates that hydantoin in aqueous and alcoholic alkaline solution undergoes amido–imidol tautomerism involving the hydrogen of the 3-position. Substitution in the 3-position is therefore easily detected. The spectra of the analogous open-chain compounds, acetylurea and hydantoic acid, are compared with that of hydantoin and the effect of the introduction of nitro- and phenyl groups into the parent ring is reported.

THE interpretation of the broad bands present in the ultra-violet absorption spectra of many organic compounds in solution is still difficult, and the underlying doubt as to whether or not data relating to such bands are of fundamental significance detracts from the value of any conclusions drawn (cf. Morton and Stubbs, *J.*, 1940, 1347). Recently attempts have been made (Chako, *J. Chem. Physics*, 1934, 2644; Förster, *Z. Elektrochem.*, 1939, **45**, 551) at mathematical treatment of such bands, and Bowen (*Ann. Reports*, 1943, **40**, 12—29) has summarised evidence relating the absorption wave-length to electronic orbital changes. The treatments are somewhat complex even for simple molecules and perhaps of greater practical value at the present are semi-empirical studies of various chromophoric groupings in attempts to arrive at generalisations (cf., *e.g.*, Booker, Evans, and Gillam, *J.*, 1940, 1453, and subsequent papers). The present paper is the first of a series in which the absorption spectra of a number of organic compounds containing nitrogen, and especially those derived from or containing the urea molecule, are to be studied.

In practically all such work the possibility of amido–imidol tautomerism, $\cdot NH\cdot CO\cdot \rightleftharpoons \cdot N{:}C(OH)\cdot$, has to be considered, and of particular interest is the effect of molecular environment on any changes in light absorption which may be associated with the tautomerism. Doubts have been expressed concerning the value of absorption spectra in assessing the molecular changes in such a system. For instance, although earlier work by Hartley and Dobbie (*J.*, 1899, **75**, 640) gave definite indications that isatin had the pseudo-isatin or lactam structure, a re-examination of the spectra by Morton and Rogers (*J.*, 1925, **127**, 2698; cf. Dabrowski and Marchlewski, *Bull. Soc. chim.*, 1933, **53**, 946; Ault, Hirst, and Morton, *J.*, 1935, 1653) showed

that the curves were too close for any reliable conclusions to be drawn. Again, although Hantzsch (*Ber.*, 1931, **64**, 664; *Z. anorg. Chem.*, 1932, **209**, 213) held that all alkali salts of such compounds were in the imidol form ·C(OR):N·, yet views have been expressed, *e.g.*, by Ramart-Lucas and Grunfeld for benzamides (*Bull. Soc. chim.*, 1937, **4**, 478), and by Ley and Specker (*Ber.*, 1939, **72**, 192), doubting the validity of conclusions drawn from the absorption spectra of substances containing the ·CO·NH· grouping, although the latter authors give values illustrating a shift towards longer wave-lengths on formation of a metal enol-salt in ordinary keto–enol tautomerism.

Nevertheless, if a further activating group is present, *e.g.*, in the case of the grouping ·CO·NH·CO·, fairly clear cut changes in the absorption spectrum can be obtained as shown for uracil (Heyroth and Loofbourow, *J. Amer. Chem. Soc.*, 1931, **53**, 3441) and other purines and pyrimidines, and for 5 : 5′-disubstituted barbituric acids (Fredholm, Thesis, Uppsala, 1939; Stuckey, *Quart. J. Pharm.*, 1941, **14**, 217; 1942, **15**, 377). Most of the hydantoin derivatives studied in the present paper contain this grouping.

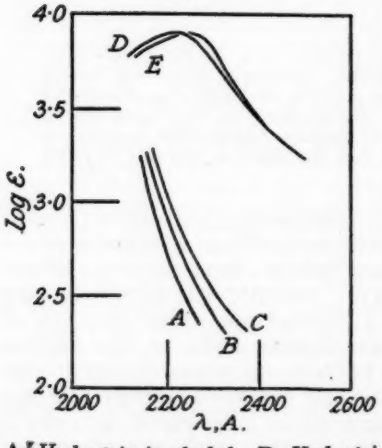
The absorption spectrum of hydantoin was measured by Asahina (*J. Chem. Soc. Japan*, 1929, **4**, 202), using an old method, although the effect of pH was not noted and no numerical results were given. The results for the hydantoin derivatives studied are shown in Figs. 1—3 and in the table.

Absorption maxima and wave-lengths.

	$\lambda_{max.}$, A.	log $\varepsilon_{max.}$		$\lambda_{max.}$, A.	log $\varepsilon_{max.}$
Hydantoin			5 : 5′-Dimethylhydantoin		
In N/100-aqueous NaOH	2230	3·90	In N/100-aqueous NaOH	2230	3·88
In N/100-alcoholic NaOEt ...	2210	3·90	1 : 5 : 5′-Trimethylhydantoin		
1-Nitrohydantoin			In N/100-aqueous NaOH ...	2310	3·91
In water and N/100-aqueous HCl	2310	3·95	Acetylurea		
In N/100-NaOH	2450	4·00	In N/10-aqueous NaOH	2220	3·11

The end absorption shown by hydantoin (Fig. 1) is little different either in alcohol or in N/100-hydrochloric acid and under both conditions Beer's law is obeyed. In N/100-aqueous alkaline solution increased absorption is shown and a broad band develops having a peak at 2230 A. A similar band develops in solutions in alcoholic sodium ethoxide. It is to be expected, in accordance with modern theory, that tautomerism would follow ionisation (*e.g.*, on dilution) and therefore that the intensity of absorption in water would increase on dilution as with barbituric acid (Stuckey, *Quart. J. Pharm.*, 1942, **15**, 370). However, the small dissociation constant of hydantoin, $K_a = 7{\cdot}59 \times 10^{-10}$ (Wood, *J.*, 1906, **89**, 1833), coupled with difficulties of measurements at wave-lengths less than 2200 A. and low extinction coefficient, made it difficult to realise any significant increase in absorption. The spectrum in M/400-aqueous solution therefore represents almost completely the un-ionised form.

FIG. 1.



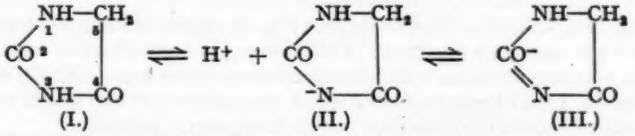
A, *Hydantoin in alcohol.* B, *Hydantoin in* N/100 *hydrochloric acid.* C, *Hydantoin,* M/400 *in water.* D, *Hydantoin in* N/100 *alcoholic sodium ethoxide.* E, *Hydantoin in* N/100 *aqueous sodium hydroxide.*

5 : 5′-Dimethylhydantoin (Fig. 2) exhibits absorption which is in general very similar to that of the parent hydantoin, with the appearance of a peak in alkaline solution. This rules out the possibility of tautomerism: ·CH_2·CO· ⇌ ·CH:C(OH)· involving groups in positions 4 and 5 since it can be fairly assumed that the characteristic absorption associated with such a change would differ from that due to amido–imidol tautomerism involving positions 1 or 3.

In a similar manner the close comparison of the absorption of 1 : 5 : 5′-trimethylhydantoin (Fig. 2) with that of hydantoin and 5 : 5′-dimethylhydantoin eliminates position 1 from the tautomerism and indicates that the only remaining ·NH· group, *i.e.*, in the 3-position, must be the one involved, producing structures (II) and (III) from the parent hydantoin.

Confirmation was obtained by the preparation and examination of 3-methylhydantoin which did *not* show the increase in absorption on changing from ordinary aqueous to alkaline solution

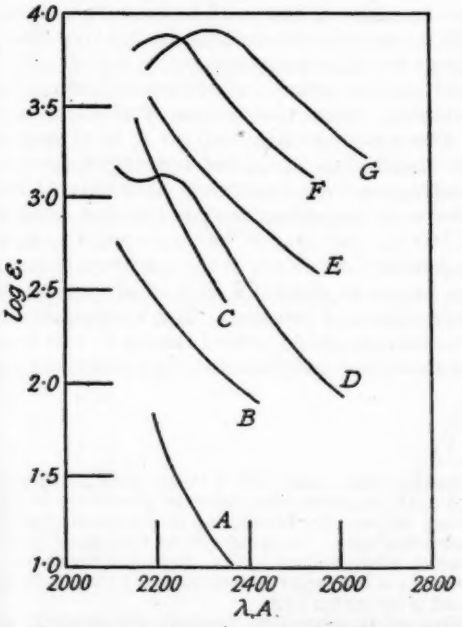
common to the other hydantoin derivatives studied. This conclusion is in agreement with the electrometric titration results of Zief and Edsall (*J. Amer. Chem. Soc.*, 1937, **59**, 2245; cf.



(I.) (II.) (III.)

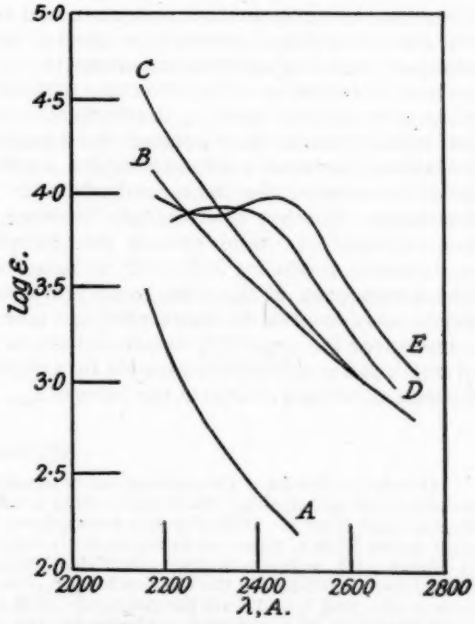
Pickett and McLean, *ibid.*, 1939, **61**, 423), who found that only the hydrogen in position 3 undergoes dissociation. The determination of absorption spectra thus affords a means of detecting substitution in the 3-position in the hydantoin ring.

FIG. 2.



A, *Hydantoic acid in water,* N/100-*hydrochloric acid, and* N/100-*sodium hydroxide.* B, *Acetylurea in water and* N/10-*hydrochloric acid.* C, 5 : 5′-*Dimethylhydantoin in water and* N/100-*hydrochloric acid.* D, *Acetylurea in* N/10-*sodium hydroxide.* E, 1 : 5 : 5′-*Trimethylhydantoin in water and* N/100-*hydrochloric acid.* F, 5 : 5′-*Dimethylhydantoin in* N/100-*sodium hydroxide.* G, 1 : 5 : 5′-*Trimethylhydantoin in* N/100-*sodium hydroxide.*

FIG. 3.



A, 3-*Methylhydantoin in water,* N/100-*hydrochloric acid, and* N/100-*sodium hydroxide.* B, 5 : 5′-*Diphenylhydantoin in water and alcohol.* C, 5 : 5′-*Diphenylhydantoin in water and alcohol.* D, *Nitrohydantoin in water and* N/100-*hydrochloric acid.* E, *Nitrohydantoin in* N/100-*sodium hydroxide.*

The peak absorption of hydantoin in alkaline solution is comparable to that developing in alkaline solutions of 5 : 5′-disubstituted barbituric acids, where the urea group amido–imidol tautomerism also occurs. Thus diethylbarbituric acid showed log $\varepsilon_{max.} = 3{\cdot}94$ at 2460 A. (Stuckey, *Quart. J. Pharm.*, 1942, **15**, 381). The end absorptions of both hydantoin and diethylbarbituric acid indicate the possibility of a peak absorption, similar to that in alkali, occurring in acid solution at wave-lengths *ca.* 2000 A. and thus not realisable under the experimental conditions used. This indicates the possibility that the effect of the tautomeric amido–imidol change on absorption spectrum is merely to shift the peak to longer wave-lengths.

Open-chain compounds analogous to hydantoin include acetylurea and hydantoic acid. The spectrum of acetylurea (Fig. 2) shows an increased and selective absorption in aqueous alkaline solution together with a shift to longer wave-lengths, and by analogy with hydantoin a urea-type amido–imidol tautomerism is indicated :

$$CH_3{\cdot}CO{\cdot}NH{\cdot}CO{\cdot}NH_2 \rightleftharpoons H^+ + CH_3{\cdot}CO{\cdot}\bar{N}{\cdot}CO{\cdot}NH_2 \rightleftharpoons CH_3{\cdot}CO{\cdot}N{:}C\bar{O}{\cdot}NH_2$$

Both acid and alkaline spectra for this substance are at a lower level than in those for hydantoin and evidently ring formation in the latter compound is responsible for a big increase in absorption *ca.* 2200 A.

Hydantoic acid, $NH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOH$ (see Fig. 2), shows the end absorption characteristic of amino-acids and has the same spectrum in alkaline as in acid solution, indicating the absence of tautomerism in aqueous solution. In this compound there is no $\cdot CO \cdot NH \cdot CO \cdot$ grouping, and it is evident that in the type of compounds studied the group $\cdot CO \cdot NH \cdot$ needs a further activating influence before amido–imidol tautomerism occurs in aqueous solution.

The introduction of two phenyl groups in the hydantoin ring, producing 5 : 5′-diphenylhydantoin, causes a general increase in absorption both in water and in acid and alkaline aqueous solution, although a characteristic acid–alkaline shift indicating tautomerism is still shown (Fig. 3).

Franchimont and Klobbie (*Rec. Trav. chim.*, 1888, **7**, 12) first prepared nitrohydantoin by the action of nitric acid on hydantoin and assigned to it the structure of 1-nitrohydantoin on the general rule that nitration occurred at the $\cdot NH \cdot$ group adjacent to CH_2, verification being obtained from ring-splitting experiments. A study of the absorption spectrum (Fig. 3) yields further confirmation of this structure in that 1-nitrohydantoin shows a shift towards the red on passing to alkaline solution, thus indicating tautomerism. Since tautomerism still occurs, the nitro-group cannot have entered the 3-position. The action of nitric acid on 5 : 5′-dimethylhydantoin produced a nitro-derivative, 1-*nitro*-5 : 5′-*dimethylhydantoin*, but 1-methylhydantoin failed to nitrate under the same conditions. The nitro-group must therefore have entered the 1-position. Further spectroscopic evidence of this may be adduced from the fact that a 5-nitrohydantoin would possess the grouping $\therefore CH \cdot NO_2$ and might be expected to show tautomerism producing $\therefore C \cdot NO \cdot OH$ accompanied by a radical difference in the spectrum change. The introduction of the nitro-group into hydantoin causes in general a shift of absorption to longer wave-lengths, so that a peak can now be realised in acid solution. This strengthens to some extent the possibility mentioned above that tautomeric amido–imidol change in this type of compound is accompanied merely by a shift of the absorption spectrum to longer wave-lengths without significant change in the value of $\varepsilon_{max.}$.

Experimental.

Absorption Spectra.—Determinations of absorption spectra were made with a Hilger medium quartz spectrograph and Spekker photometer using a condensed spark between tungsten-steel electrodes as the normal light source. Difficulty was experienced in getting satisfactory blackening of the photographic plate below 2300 A. unless an inconveniently long exposure was used. To some extent the use of Ilford Q Plates with uranium–copper electrodes helped to solve this problem. The molecular extinction coefficient ε is defined by the relation $\log_{10} I_0/I = \varepsilon cl$, where c is the molar concentration, l the length of tube in cm., and I_0 and I are the intensities of incident and transmitted light.

Preparation of Compounds.—Owing to the possibility of tautomerism, unequivocal methods of preparation were essential for the methylated hydantoins. Compounds not specifically mentioned were purified by recrystallisation from alcohol before determination of their light absorption.

1 : 5 : 5′-*Trimethylhydantoin.* Biltz and Slotta (*J. pr. Chem.*, 1926, **113**, 240) prepared this substance from α-methylamino*iso*butyronitrile *via* *N*-methyl-*N*′-(α-cyano*iso*propyl)urea and record it as difficult to crystallise, giving no m. p. It was found that, after removal of water by several evaporations with absolute alcohol, the substance crystallised from this solvent and had m. p. 160° (corr.) (Found : C, 50·7; H, 7·0. Calc. for $C_6H_{10}O_2N_2$: C, 50·1; H, 7·0%).

5 : 5′-Dimethylhydantoin was prepared similarly from α-amino*iso*butyronitrile and crystallised from absolute alcohol. Methylation of hydantoin in sodium hydroxide solution with methyl sulphate was used for the preparation of 3-methylhydantoin, the constitution of the product having previously been established (Biltz and Slotta, *loc. cit.*; Harries and Weiss, *Annalen*, 1903, **327**, 355).

1-*Nitro*-5 : 5′-*dimethylhydantoin.* 5 : 5′-Dimethylhydantoin (1·0 g.) and concentrated nitric acid (10 c.c.) were evaporated to a syrup on a water-bath. After cooling, absolute alcohol (20 c.c.) was added, the mixture boiled and filtered, and the filtrate evaporated to crystallisation. Recrystallisation from absolute alcohol gave white crystals, m. p. 143—144° (not sharp) (Found : C, 33·9; H, 4·2. $C_5H_7O_4N_3$ requires C, 34·7; H, 4·1%). At temperatures above the m. p. decomposition occurred with the evolution of bubbles of gas. The *compound* is sparingly soluble in alcohol, but soluble in water.

1-Nitrohydantoin was prepared following the method of Franchimont and Klobbie (*loc. cit.*).

Home Office Forensic Science Laboratory, Preston. [*Received, June 25th*, 1946.]

65. *Thiosulphate Complexes of the Tervalent Metals, Iron, Aluminium, and Chromium.*

By N. Uri.

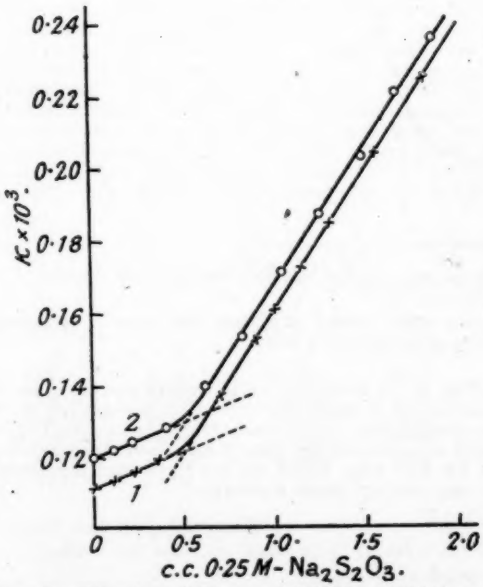
It has been demonstrated for the first time that there exist complex compounds of Al^{+++} and Cr^{+++} with $S_2O_3^{--}$. These complexes have the general composition $[M^{III}(S_2O_3)]^+$. Furthermore it has been shown that the violet intermediate compound in the reaction of $S_2O_3^{--}$ with Fe^{+++} is the complex anion $[Fe(S_2O_3)_2]^-$.

The existence of complex thiosulphates of Al^{+++} and Cr^{+++} has not previously been demonstrated. Attempts to isolate such compounds have invariably failed owing to hydrolysis, leading to the precipitation of the hydroxides, and even in solution their existence has not been proved. By the choice of suitable conditions (low temperature and high concentration of ethyl alcohol) the degree of hydrolysis could be lowered to such an extent that it became possible to prove that thiosulphate complexes of the above metals indeed exist in solution. We also investigated the violet thiosulphate complex of Fe^{+++} whose composition has been disputed. Holluta and Martini (*Z. anorg. Chem.*, 1924, **140**, 206) studied the kinetics of the reaction between Fe^{+++} and thiosulphate and concluded that as the first stage an anion-complex $[Fe(S_2O_3)_2]^-$ is formed immediately, which later reacts slowly with a further Fe^{+++} ion to give Fe^{++} and $S_4O_6^{--}$. Schmid (*Z. physikal. Chem.*, 1930, *A*, **148**, 321) on the other hand investigated the problem by potentiometric measurements in flowing solutions and inferred that the intermediate compound consisted of a cation complex $[Fe(S_2O_3)]^+$. Our results support the former view.

Experimental.

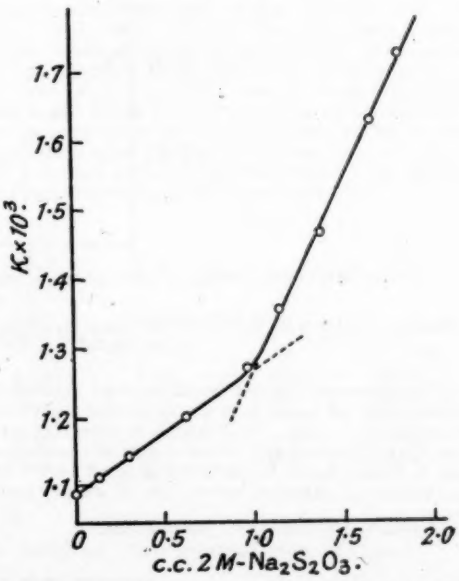
The conductometric method was used to prove the existence and composition of the complex compounds. The measurements were carried out by using a lyograph (" Lautenschläger ") : full detail

Fig. 1.



Curve 1 : *Titration of* 50 *c.c. of* 0·0025M-$Al(NO_3)_3$ *in* 70% (*vol.*) *ethyl alcohol at* 0° *with an aqueous solution of* 0·25M-$Na_2S_2O_3$. *Curve* 2 : *Titration of* 50 *c.c. of* 0·0025M-$Cr(NO_3)_3$ in 70% (*vol.*) *ethyl alcohol at* 0° *with an aqueous solution of* 0·25M-$Na_2S_2O_3$.

Fig. 2.



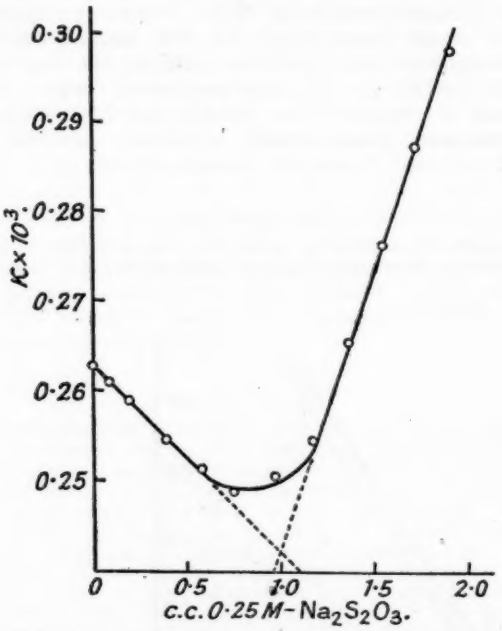
Titration of 50 *c.c. of* 0·02M-$Fe(NO_3)_3$ *in* 50% (*vol.*) *ethyl alcohol at* 0° *with an aqueous solution of* 2M-$Na_2S_2O_3$. *Duration of titration* : 2 *mins.*

are given by Bobtelsky and Simchen (*J. Amer. Chem. Soc.*, 1942, **64**, 454). After a number of titrations, the optimum working conditions were found to be a temperature of 0° and an ethyl alcohol concentration of 70% by volume. Higher concentrations of alcohol lower the solubility of sodium thiosulphate to such an extent that the difficulty of carrying out accurate measurements becomes excessive. The

conductometric titration curves shown in Fig. 1 (curves 1 and 2) establish the complete analogy between Cr^{+++} and Al^{+++}. In both cases we have distinct breaks corresponding to a ratio 1 M^{+++} : 1 $S_2O_3^{--}$.

The situation is somewhat different in the case of Fe^{+++}. It is well known that in the reaction between Fe^{+++} and $S_2O_3^{--}$ an unstable violet intermediate compound is formed at once and quickly decomposes to give the final products Fe^{++} and $S_4O_6^{--}$. The main difficulty in the investigation of this intermediate compound by conductometric titration lies in its very short life at room temperature. By the addition of ethyl alcohol and by lowering the temperature, the stability of the intermediate compound could be increased considerably, but nevertheless it was essential to use an apparatus which enabled titrations to be carried out within 2 minutes. To make sure that no appreciable decomposition had occurred within these 2 minutes, a few isolated points on the titration curves were checked by the rapid addition of the requisite quantity of reagent from the burette. Excellent agreement was invariably obtained between these values (whose measurement occupied only 30 secs.) and those obtained in the actual titration. The titration curves (Figs. 2 and 3) show distinct breaks corresponding to a ratio 1 Fe^{+++} : 2 $S_2O_3^{--}$. Back titrations (with the thiosulphate in the conductivity cell and the ferric salt solution in the burette) led to analogous results. This confirms Hollutta and Martini's view that an anion complex $[Fe(S_2O_3)_2]^-$ is formed as an intermediate compound.

FIG. 3.



Titration of 50 *c.c. of* 0·0025M-$Fe(NO_3)_3$ *in* 70% (*vol.*) *ethyl alcohol at* 0° *with an aqueous solution of* 0·25M-$Na_2S_2O_3$. *Duration of titration* : 2 *mins.*

The above-mentioned break is most marked in Fig. 3. This is due to an anomalous effect in the conductivity of ferric ions at different concentrations of ethyl alcohol observed by the author in the course of this work. It is hoped to investigate this point later. At a concentration of about 70% of alcohol the conductivity of ferric nitrate passes through a maximum and thus it can be easily understood that in consequence of the exchange of Fe^{+++} ions by Na^+ ions, which do not show such anomalous behaviour, the titration curve falls off steeply and a very distinct break is obtained.

HEBREW UNIVERSITY, JERUSALEM. [*Received, July 2nd,* 1946.]

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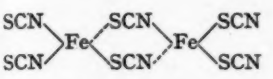
66. *The Ferric Thiocyanate Complex in Ethyl-alcoholic Solution.*

By N. URI.

It is proved by conductometric measurements that only one complex compound between Fe^{+++} and SCN^- exists in alcoholic solution, the ratio being 1 Fe : 3 SCN. The most probable structure is that of a polynuclear complex compound. The cation complexes $Fe(SCN)^{++}$ and $Fe(SCN)_2^+$, which have recently been proved to exist in aqueous solution, do not occur in ethyl-alcoholic solution.

VARIOUS theories have been put forward concerning the structure of the ferric thiocyanate complex whose intense red colour is used for the photometric determination of iron. For a long time this red colour was thought to be due to undissociated $Fe(SCN)_3$ molecules. In 1931 Schlesinger and van Valkenburgh (*J. Amer. Chem. Soc.*, **53**, 1212) concluded that the colour was due to the anion complex $Fe(SCN)_6^{---}$; and Brintzinger and Ratanarat (*Z. anorg. Chem.*, 1935, **223**, 106) assumed, on the basis of their dialysis coefficient measurements, that the compound was an anion complex. However, recent workers (Møller, *Kem. Maanedsblad*, 1937, **18**, 138; Bent and French, *J. Amer. Chem. Soc.*, 1941, **63**, 568) proved conclusively (especially by photometric measurements) that in the reaction between ferric and thiocyanate ions the complex cations $[Fe(SCN)]^{++}$ and $[Fe(SCN)_2]^{+}$ were formed. The author's conductometric measurements confirmed their existence in aqueous solution only. In ethyl alcohol, on the other hand, the measurements show that there exists only one complex compound, and this in the ratio 1 Fe : 3 SCN.

Since it is known that ferric thiocyanate in alcoholic solution has a molecular weight corresponding to $Fe_2(SCN)_6$, and that it exhibits the properties of polynuclear complexes (*e.g.*, high solubility in organic solvents), the most probable formula for this substance is that proposed by Schlesinger (*ibid.*, 1941, **63**, 1765) (see inset), and this is in complete analogy to the now generally accepted structure of ferric chloride.



EXPERIMENTAL.

The conductometric measurements were not carried out by titrations, since the insufficient solubility of the titrant reagent in alcohol would impair the accuracy owing to the dilution effect; instead, separate conductivity measurements at different concentrations were taken. Since we wished to work with concentrated solutions we used a special cell for which only 2 c.c. of solution were required. This cell consisted essentially of two parallel platinised platinum electrodes 2 cm. apart contained in a Pyrex tube of 5 mm. diameter. The conductivity was measured by means of a Wheatstone bridge with end-coils and a Leeds & Northrup a.c. galvanometer as null-point instrument. The experimental error in these conductometric measurements was within $\pm$ 0·2%. Table I shows the specific conductivity (κ) of solutions of constant concentration of ammonium thiocyanate (0·5M) and various concentrations of ferric nitrate (nonahydrate). The solvent was 96% (by vol.) ethyl alcohol. The experiments were carried out in a thermostat at 30°. The conductivities were measured immediately after the preparation of the solutions to avoid errors which might be caused by the slow oxidation of the ethyl alcohol to acetaldehyde by ferric ions. It is evident from the values given in Table I that the conductometric curve has a break at 1Fe : 3SCN. The measurements shown in Table II were at 0° and with a constant concentration (0·1M) of ferric nitrate and varied concentrations of ammonium thiocyanate, the solvent being the same as before. Here, too, where the concentration ratio changes in the opposite direction, the results show only the one break at 1Fe : 3SCN and do not indicate the existence of any cation complex. The structure of the compound is satisfactorily explained by Schlesinger's formula.

TABLE I.

Conductivity measurements at 30° *in ethyl alcohol* (96% *vol.*) *at a constant concentration of* 0·5M-NH_4SCN.

$Fe(NO_3)_3$, M.	$\kappa \times 10^3$.	$Fe(NO_3)_3$, M.	$\kappa \times 10^3$.	$Fe(NO_3)_3$, M.	$\kappa \times 10^3$.	$Fe(NO_3)_3$, M.	$\kappa \times 10^3$.
0·0	11·25	0·0750	9·79	0·1375	8·76	0·30	10·31
0·0125	10·99	0·0875	9·55	0·1500	8·70	0·35	11·12
0·0250	10·73	0·1000	9·32	0·1750	8·66	0·40	11·94
0·0375	10·48	0·1125	9·10	0·20	8·76	0·45	12·66
0·0500	10·27	0·1250	8·92	0·25	9·52	0·50	13·34
0·0625	10·03						

TABLE II.

Conductivity measurements at 0° *in ethyl alcohol* (96% *vol.*) *at a constant concentration of* 0·1M-$Fe(NO_3)_3$.

NH_4SCN, M.	$\kappa \times 10^3$.	NH_4SCN, M.	$\kappa \times 10^3$.	NH_4SCN, M.	$\kappa \times 10^3$.	NH_4SCN, M.	$\kappa \times 10^3$.
0·0	1·904	0·100	2·275	0·200	2·647	0·50	4·792
0·025	2·004	0·125	2·367	0·25	2·831	0·60	5·724
0·050	2·098	0·150	2·461	0·30	3·026	0·70	6·698
0·075	2·185	0·175	2·558	0·40	3·899	0·80	7·581

HEBREW UNIVERSITY, JERUSALEM. [*Received, July 2nd*, 1946.]

67. *The Constitution of Yeast Ribonucleic Acid. Part XI. Synthesis of Uridine-2′ Phosphate.*

By J. Masson Gulland and H. Smith.

Uridine-2′ phosphate has been synthesised by procedures which define clearly the position of the phosphoryl group. It follows, therefore, that uridylic and cytidylic acids are 3′-phospho-derivatives of the nucleosides, as postulated hitherto without proof. The stabilities of uridine-2′ phosphate and uridylic acid towards alkali are closely similar, and thus give rise to the view that the facile alkaline fission of yeast ribonucleic acid is not due to a marked and inherent lability of the ester linkage in position 2′, but is a property of the polynucleotide. The significance of these observations is discussed.

It was postulated by Levene and Tipson (*J. Biol. Chem.*, 1935, **109**, 623) that phospho-ester groups at C2′ of the ribonucleosides would be labile, and that the presence of these linkages in ribonucleic acid would account for the ease with which the polynucleotide suffers hydrolysis in cold dilute alkaline solution. This postulate has been accepted by others (Makino, *Z. physiol. Chem.*, 1935, **236**, 201; Bredereck, *Fortschr. Chem. Org. Naturstoffe*, 1938, **1**, 152). No nucleoside-2′ phosphate however has, as yet, either been identified among the fission products of yeast ribonucleic acid or been prepared synthetically; the behaviour of such compounds towards hydrolytic agents has therefore been a matter of conjecture, although Gulland and Walsh (*J.*, 1945, 172) have pointed out that there is no record of substituents in the hydroxyls of carbohydrates differing so markedly in stability as to explain the complete fission of an ester at C2′ whilst a similar linkage at C3′ remains unattacked.

The sugar of uridine was shown to be in furanose form by Levene and Tipson (*J. Biol. Chem.*, 1933, **101**, 529), and the same authors prepared and characterised uridine-5′ phosphate by phosphorylating its 2′ : 3′-*iso*propylidene derivative (*ibid.*, 1934, **106**, 113).

Uridylic acid, obtained by alkaline fission of yeast ribonucleic acid, is different from uridine-5′ phosphate and is therefore uridine-2′ or -3′ phosphate. By analogy with the purine nucleotides, in which the phosphoryl group was proved to esterify the hydroxyl at C3′ (Levene and Harris, *ibid.*, 1932, **98**, 9; Levene, Harris, and Stiller, *ibid.*, 1934, **105**, 153), it has been generally assumed without proof that uridylic acid, and hence cytidylic acid, which can be converted into uridylic acid by deamination (Bredereck, *Z. physiol. Chem.*, 1934, **224**, 79), are 3′-phospho-esters of the corresponding nucleosides. Uridylic acid was synthesised by phosphorylation of uridine in barium hydroxide solution (Gulland and Hobday, *J.*, 1940, 746) and of 5′-trityl uridine (Bredereck and Berger, *Ber.*, 1940, **73**, 1124), but these syntheses shed no light on the choice between positions 2′ and 3′. Through the synthesis of uridine-2′ phosphate now described, and the demonstration that this nucleotide is different from uridylic acid, it is proved that uridylic and cytidylic acids are 3′-phospho-esters of the nucleosides.

3′ : 5′-*Benzylidene uridine* (I, R = H) was prepared in good yield by condensation of uridine with benzaldehyde in the presence of zinc chloride. The allocation of the benzylidene group to these positions is deduced as follows. It is known (Haworth and Hirst, *Ann. Rev. Biochem.*, 1936, **5**, 83) that benzaldehyde condenses readily with alternate, but rarely with adjacent, hydroxyl groups of a sugar, and on stereochemical considerations condensation will not occur with hydroxyl groups at C2′ and C5′ of the *d*-ribose residue. The remote possibility that the sugar might have changed from the furanose to the pyranose form during the condensation in presence of zinc chloride was ruled out by recovery of uridine from benzylidene uridine after hydrolysis with dilute acid; the presence of the furanose ring in the recovered and the original uridine was confirmed by periodate titrations (Lythgoe and Todd, *J.*, 1944, 592). If, after phosphorylation of benzylidene uridine and removal of the benzylidene radical, a nucleotide were obtained differing from uridine-5′ phosphate and from uridylic acid, that nucleotide would be a 2′-phospho-ester, benzylidene uridine would be the 3′ : 5′-derivative, and uridylic acid would be a 3′-phospho-ester. The differences expected were realised in fact, and these conclusions are therefore valid.

Phosphorylation of benzylidene uridine with diphenyl chlorophosphonate* in anhydrous pyridine gave a good yield of 3′ : 5′-*benzylidene uridine-2′ diphenyl phosphate* [I, R = $(PhO)_2PO$·]. Hydrolysis of this substance with N/2-sodium hydroxide solution at 100° for 30 minutes yielded benzylidene uridine phenyl phosphate, which was converted directly by hydrolysis with hot

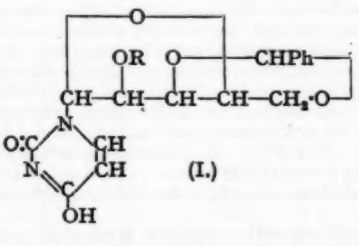
* The term diphenyl chlorophosphonate is here used in place of diphenylphosphoryl chloride used previously (*J.*, 1940, 746) in view of a recent decision that $PO(OH)_2Cl$ should be called chlorophosphonic acid by analogy with corresponding compounds of sulphur and other elements.

N/4-sulphuric acid into *uridine-2′ phenyl phosphate* (II, R = Ph). This was characterised as the *brucine* salt and was further proved to be a di-ester by electrometric titration and estimation of one molecular equivalent of phenol after fission with hot 10N-sodium hydroxide. This graded hydrolysis of 3′ : 5′-benzylidene uridine-2′ diphenyl phosphate is in contrast with the complete dephenylation of diphenylphosphoryl derivatives of uridine, cytidine, and adenosine through the action of N/2-sodium hydroxide for 30 minutes as recorded by Bredereck, Berger, and Ehrenberg (*Ber.*, 1940, **73**, 269) and Bredereck and Berger (*ibid.*, p. 1124).

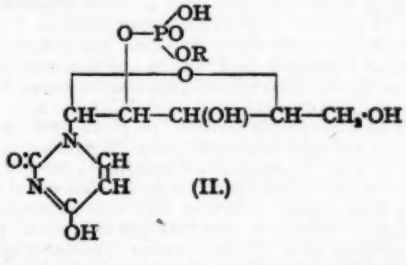
Determinations of free phenol and inorganic phosphate during hydrolysis of 3′ : 5′-benzylidene uridine-2′ diphenyl phosphate with N-sodium hydroxide at 100° showed that the second phenyl group was liberated at the same rate as dephosphorylation and formation of inorganic phosphate. Hydrogenolysis with platinum oxide and hydrogen at room temperature and pressure readily removed the residual phenyl radical from uridine-2′ phenyl phosphate; in these mild conditions reduction of the uracil radical did not occur (cf. Levene and La Forge, *Ber.*, 1912, **45**, 608; Levene and Jorpes, *J. Biol. Chem.*, 1929, **81**, 579; Levene and Tipson, *ibid.*, 1934, **106**, 113; Brown and Johnson, *J. Amer. Chem. Soc.*, 1923, **45**, 2702).

Uridine-2′ phosphate (II, R = H) was thus obtained in good yield and characterised as the *barium* and *brucine* salts. It was shown to be different from uridylic acid and from uridine-5′ phosphate by comparisons of the acid hydrolysis curves of the three nucleotides, of the conditions of precipitation of their lead salts, of the solubilities of their barium salts, and of the crystalline forms, solubilities, melting points, and rotations of their brucine salts.

Uridine-2′ phosphate was stable for 3 days in 1% sodium hydroxide solution at room temperature, and comparison of its alkaline hydrolysis curve with that of uridylic acid showed that the phosphoryl group of the synthetic acid was only slightly more labile than that of the natural nucleotide. The difference, as such, was totally inadequate to account for the supposed complete fission of the ester linkage at C2′ and stability of that at C3′.



(I.)



(II.)

In the light of this communication, the instability of the internucleotide linkage is a characteristic of the polynucleotide structure, and not an inherent property of the ribose-2′ phosphoester group as postulated by Levene and Tipson. Two possibilities must be considered. Either the alkaline fission of yeast ribonucleic acid leads solely, as hitherto postulated, to the formation of 3′-phospho-nucleosides, or it produces a mixture of nucleosides phosphorylated at C3′ and also at C2′ (or C5′).

As regards the former alternative, some factor must operate to promote the instability of the phosphoryl group which is not at C3′. An unorthodox speculation as to the nature of this factor is that the sugar radicals of the polynucleotide are not in the furanose form as found in the nucleosides, but are 1 : 2-glycosides doubly esterified by phosphoryl groups at C3′ and C4′, the lability of this ring as compared with the stability of the furanose form providing a driving force which results in the extrusion of the phosphoryl at C4′.

In the case of the latter alternative, it may be recalled that yields of 3′-phospho-nucleosides isolated from the fission of yeast ribonucleic acid have always fallen short of the theoretical. The triply esterified phosphoryl groups of the polynucleotide (Fletcher, Gulland, and Jordan, *J.*, 1944, 33) could be expected to exhibit increased alkali lability as compared with the phosphoryl groups of mononucleotides by analogy with other phosphoryl tri-esters (Lossen and Kohler, *Annalen*, 1891, **262**, 209; Drushel, *Amer. J. Sci.*, 1915, **40**, 643; Drushel and Felty, *ibid.*, 1917, **43**, 57; Autenrieth, *Ber.*, 1897, **30**, 2369; Cavalier, *Compt. rend.*, 1898, **127**, 114; Plimmer and Burch, *J.*, 1929, 279); the behaviour of 3′ : 5′-benzylidene uridine-2′ diphenyl phosphate on hydrolysis conforms to the general pattern. Phosphoryl di-esters, however, are more stable towards alkaline hydrolysis, but it is relevant to refer to the quantitative conversion of αβ-diglyceryl monophosphate into α- and β-monoglyceryl phosphoric acids, without liberation of inorganic phosphate, as a result of hydrolysis by one molar proportion of sodium hydroxide

in dilute solution (Bailly and Gaumé, *Bull. Soc. chim.*, 1926, **39**, 1420; *Compt. rend.*, 1926, **183**, 67). It is possible that the lability of a phosphoryl ester towards alkali might be increased by the presence of a second phosphoryl ester at the adjacent carbon atom.

The syntheses of other 2′-phospho-nucleosides will be reported shortly, and the alternatives outlined above are being investigated.

Experimental.

Uridine, colourless needles, m. p. 164—165°, $[\alpha]_D^{20°}$ + 4·8°, was prepared from yeast ribonucleic acid by combining the procedures of Bredereck (*Ber.*, 1941, **74**, 694) and of Gulland and Hobday (*J.*, 1940, 746).

3′:5′-*Benzylidene Uridine.*—A mixture of uridine (10 g.), dried at 100° over phosphoric oxide in a vacuum for 4 hours, zinc chloride (15 g.), and freshly distilled benzaldehyde (50 c.c.) was shaken at room temperature for 12 hours. After standing for 48 hours, the clear brown solution was poured into ether (500 c.c.) in a separating funnel and zinc chloride was extracted by successive small quantities of water. After the ethereal suspension had remained at 0° for 3 hours, crude *benzylidene uridine* (11·3 g.) was collected, washed with ether, and crystallised repeatedly from water (65 parts), from which it (8·4 g.) separated in colourless needles, m. p. 189—190° (Found, in anhydrous material: C, 57·8; H, 4·9; N, 8·5. $C_{16}H_{16}O_6N_2$ requires C, 57·8; H, 4·9; N, 8·4%).

Uridine was regenerated by hydrolysis of benzylidene uridine (1 g.) at 100° for ¾ hour with N/4-sulphuric acid (100 c.c.). After removal of the benzaldehyde by extraction with ether, and of the sulphuric acid by means of baryta, the solution was evaporated to a syrup which was dissolved in hot absolute alcohol (10 c.c.). On cooling, uridine crystallised in colourless needles, m. p. 164—165°, $[\alpha]_D^{20°}$ + 4·6°; a mixed m. p. with authentic uridine was not depressed. This material absorbed 0·98 mol., and the original uridine 0·99 mol., of sodium metaperiodate per mol. No formic acid was liberated in either case.

3′:5′-*Benzylidene Uridine-2′ Diphenyl Phosphate.*—A solution of freshly distilled diphenyl chlorophosphonate (2·75 c.c.) (Brigl and Müller, *Ber.*, 1939, **72**, 2121) in dry pyridine (14 c.c.) was added during 15 minutes to a mechanically stirred solution of dry benzylidene uridine (2·75 g.) in dry pyridine (33 c.c.), cooled in an ice–salt mixture and protected from moisture. Stirring was continued for 2 hours in the freezing mixture and for 1 hour at room temperature; the solution was again cooled, water (8 c.c.) added during 15 minutes, and stirring continued for 1 hour. The yellow oil which separated when the mixture was poured into ice-water (300 c.c.) was extracted with chloroform, and the solution washed successively with dilute sulphuric acid, water, sodium bicarbonate, water, and then evaporated completely under reduced pressure. The residual gum was dissolved in ice cold N/10-sodium hydroxide, and the solution filtered and neutralised exactly with N/10-sulphuric acid. 3′:5′-*Benzylidene uridine-2′ diphenyl phosphate* separated as an amorphous powder, m. p. 56—60° (4·0 g.), which was washed by decantation, collected, and dried in a vacuum desiccator over phosphoric oxide (Found, on anhydrous material: C, 59·6; H, 4·6; N, 4·9; P, 5·4. $C_{28}H_{25}O_9N_2P$ requires C, 59·6; H, 4·5; N, 5·0; P, 5·5%). It formed an intensely yellow solution in cold alkali which faded on removal of the first phenyl radical (see below). It dissolved readily in the usual organic solvents, but was sparingly soluble in carbon tetrachloride and insoluble in light petroleum. Attempts to crystallise it have so far failed.

Hydrolysis of 3′:5′-*Benzylidene Uridine-2′ Diphenyl Phosphate with* N-*Sodium Hydroxide.*—A flask containing the compound (48 mg.) and N-sodium hydroxide (2 c.c.) was heated to 100°, closed, and left in a boiling water-bath. At intervals, small quantities of the hot solution were removed and cooled rapidly to room temperature, and determinations of inorganic phosphate (Briggs, *J. Biol. Chem.*, 1922, **53**, 13) and of free phenol (Folin and Ciocalteu, *ibid.*, 1927, **73**, 627) were made on samples (0·1 c.c.). For the determination of free phenol, the sample was acidified with tartaric acid and steam-distilled. The following table records the molar equivalents of phosphate and phenol liberated per mol. of 3′:5′-benzylidene uridine-2′ diphenyl phosphate:

Time, hours	0·5	1·0	1·5	2·0	4·0
Inorganic phosphate, mols.	0	0·06	0·09	0·13	0·25
Free phenol, mols.	1·00	1·09	1·11	1·12	1·25

Uridine-2′ Phenyl Phosphate.—3′:5′-Benzylidene uridine-2′ diphenyl phosphate (1·4 g.) and N/2-sodium hydroxide (50 c.c.) were heated at 100° for 30 minutes, N-sulphuric acid (50 c.c.) was added, and the heating continued for 45 minutes. After the phenol and benzaldehyde had been extracted with ether, the mixture was neutralised with sodium hydroxide, mixed with a slight excess of 25% barium acetate to precipitate sulphate ions, diluted to 300 c.c., and mixed with 25% lead acetate solution and sufficient ammonia to adjust the reaction to pH 9; the lead salt was not precipitated at pH 6·8—7·0. The lead salt was centrifuged, washed, and decomposed with hydrogen sulphide, and the solution, after being freed from lead sulphide by filtration and from hydrogen sulphide by aeration, was made alkaline to litmus with a 10% solution of brucine in alcohol, and evaporated to a syrup. This was dissolved in hot water (5 c.c.), filtered, and left in a refrigerator until a small quantity of brucine had separated and been removed. The solution was evaporated to a syrup, mixed with alcohol, and poured into ether. The resulting precipitate of *brucine* salt separated in micro-crystalline form from 97% alcohol. When dried for 48 hours at 15 mm. over phosphoric oxide, placed in a bath at 213°, and heated at 4° per min., slight shrinkage occurred at 218°, and at 222—225° the salt melted to a transparent liquid (Found, in material dried at 60° and 0·25 mm.: C, 57·5; H, 5·7; N, 6·9; P, 3·9; brucine, 51·2. $C_{22}H_{26}O_4N_2,C_{15}H_{17}O_9N_2P$ requires C, 57·4; H, 5·5; N, 7·0; P, 3·9; brucine, 49·6%. Loss, 2·4% of dry weight; H_2O requires 2·3%). Material dried as for analysis had $[\alpha]_D^{24°}$ — 31·5° in dry pyridine (*c*, 0·99). Potentiometric titration of, and estimation of total phenol (liberated by 10N-sodium hydroxide at 100° in 4 hours) in a solution of

the acid, prepared by decomposition of the lead salt with hydrogen sulphide, showed that one phosphoryl dissociation and one phenol radical per mol. were present.

Uridine-2′ Phosphate.—3′:5′-Benzylidene uridine-2′ diphenyl phosphate (3·7 g.) and N/2-sodium hydroxide (140 c.c.) were heated at 100° for 30 minutes, N-sulphuric acid (140 c.c.) was added, and the heating continued for 45 minutes. After extraction of the phenol and benzaldehyde with ether, N-sodium hydroxide (69 c.c.) was added, and the solution evaporated under reduced pressure to about 35 c.c., and mixed with industrial methylated spirit (350 c.c.) to precipitate sodium sulphate, which was collected. The filtrate and washings were evaporated to a small volume under reduced pressure, diluted with water, and evaporated to 30 c.c. When this solution was shaken in 1 atm. of hydrogen at room temperature for 4½ hours with Adams's platinum oxide (0·5 g., added in three batches), absorption took place of 95% of the volume of hydrogen theoretically required for hydrogenolysis of the phenyl ester. The solution was filtered from the catalyst, mixed with a little barium acetate to remove sulphate ions, and then with lead acetate solution and ammonia to adjust the reaction to pH 6·8—7·0. The lead salt was separated (centrifuged), washed, and decomposed with hydrogen sulphide, and the solution filtered, aerated, concentrated under reduced pressure to 30 c.c., and mixed with saturated barium hydroxide solution till alkaline to phenolphthalein. Excess of barium hydroxide was removed from the solution by passage of carbon dioxide, boiling, cooling, and filtering, and the resulting solution was concentrated to 25 c.c. and mixed with absolute alcohol (50 c.c.). The solid was collected, washed with 66% alcohol, 95% alcohol, and ether, and dried in a vacuum. It was purified by solution in water, filtration and reprecipitation. The *barium* salt (1·6 g.) formed a white amorphous powder, readily soluble in water (Found, in two batches of anhydrous material: P, 6·7, 6·8; Ba, 30·9, 31·6. $C_9H_{11}O_9N_2PBa$ requires P, 6·8; Ba, 29·9%). The salt contained no inorganic phosphate, *e.g.*, barium phosphate, and all attempts failed to bring the barium analytical figures closer to those theoretically required.

The *dibrucine* salt was prepared from the barium salt (1·4 g.) by removing the barium quantitatively from an aqueous solution by means of N/10-sulphuric acid, adding an alcoholic solution of brucine (2·1 mols.), and evaporating the mixture to dryness under reduced pressure. The salt was crystallised twice from 35% alcohol (8 parts) and twice from water (18 parts), from which it separated in irregular, coarse prisms (2·3 g.); the m. p. (see below) was not changed by three more recrystallisations from water (Found, in material dried at 60° and 0·25 mm.: C, 59·5; H, 6·1; N, 7·5; P, 2·8; brucine, 73·2. $C_9H_{13}O_9N_2P,2C_{23}H_{26}O_4N_2$ requires C, 59·3; H, 5·9; N, 7·6; P, 2·8; brucine, 70·8%. Loss 7·5% of dry weight; $4·5H_2O$ requires 7·3%).

Dibrucine Uridylate and Uridine-5′ Phosphate.—These salts were required for comparison. The former salt was prepared from yeast ribonucleic acid by a modification of the method of Bredereck and Richter (*Ber.*, 1938, **71**, 718) to be published shortly, and crystallised four times from 33% alcohol (Found, in material dried at 60° and 0·25 mm.: C, 59·1; H, 6·1; N, 7·6; P, 2·8. Calc. for $C_9H_{12}O_9N_2P,2C_{23}H_{26}O_4N_2$, C, 59·3; H, 5·9; N, 7·6; P, 2·8%). The latter salt was a sample prepared by Gulland and Hobday (*J.*, 1940, 746).

Comparisons of Uridylic Acid, Uridine-5′ Phosphate, and Uridine-2′ Phosphate.—(i) *Hydrolysis in N/10-sulphuric acid.* The percentage dephosphorylations given for uridylic acid and uridine-5′ phosphate are the means of those recorded by Levene and Tipson (*J. Biol. Chem.*, 1934, **106**, 113) and Gulland and Hobday (*loc. cit.*). The dephosphorylation of uridine-2′ phosphate was determined as follows. A solution of the dibrucine salt (equivalent to about 0·18 g. of anhydrous material) in hot water (20 c.c.) was cooled, and before crystallisation began barium hydroxide solution (5 c.c.; equivalent to 2·20 c.c. of 1·020N-sulphuric acid) was added. Brucine was extracted by five successive portions (each 15 c.c.) of chloroform, 1·020N-sulphuric acid (2·40 c.c.) was added, and the precipitated barium sulphate centrifuged off and washed. The combined centrifugate and washings, together with 1·020N-sulphuric acid (9·61 c.c.), were diluted with water to 100 c.c. The total phosphorus in 5 c.c. of this solution was 0·238 mg. (average of 4 concordant estimations). Samples (5·0 c.c.) were sealed in tubes and placed in a boiling water-bath. At intervals two tubes were removed and cooled rapidly, and the inorganic phosphate of the contents determined. The variation between these duplicates never exceeded 3% and the mean figure is quoted.

	P, mg./10 c.c. N/10-acid.	Time, hrs.	2.	4.	6.	8.	20.	24.	28.	30.
2′-Phosphate	0·48	Inorg. P, mg./5 c.c.	0·012	0·019	0·025	0·032	0·067	0·076	0·092	0·097
		Dephosph., %	5·0	8·0	10·5	13·4	28·2	32·0	38·6	40·7
5′-Phosphate	0·50, 0·60	Dephosph., %	3·0	5·5	7·5	9·5	19·5	23·0	26·0	28·0
3′-Phosphate	0·35, 0·40, 0·62	Dephosph., %	15·0	25·0	33·5	40·0	68·0	74·0	79·0	81·0

(ii) *Hydrolysis in N/10-sodium hydroxide.* A solution of brucine salt (equivalent to about 0·18 g. of anhydrous material) in hot water (50 c.c.) was cooled, and before crystallisation began 1·033N-sodium hydroxide (3·0 c.c.) was added. Brucine was extracted by five successive portions of chloroform (15 c.c. each), the solution was filtered to remove chloroform drops and, with the addition of 1·033N-sodium hydroxide (7·0 c.c.), diluted to 100 c.c. with water. Total phosphorus was determined in three samples (2 c.c.), and the absence of inorganic phosphate was shown by analysis of two samples (5 c.c.). The remainder of the solution was transferred to a flask fitted with an efficient condenser, heated rapidly to boiling and immersed in a boiling water-bath. At intervals samples of the hot liquid were removed and cooled rapidly, and the inorganic phosphate determined in duplicate (Briggs, *loc. cit.*). A slight greenish tint in the colour developed decreased the accuracy of the determinations, and the duplicates had a maximum variation of 8%; mean figures are quoted.

	P, mg./5 c.c. N/10-NaOH.	Time, hrs.	1.	2.	3.	4.	5.	6.	7.	8.
3′-Phosphate	0·259	Inorg. P, mg./5 c.c.	0·007	0·012	0·018	0·024	0·028	0·035	0·040	0·046
		Dephosph., %	2·7	4·6	6·9	9·3	10·8	13·5	15·5	17·8
2′-Phosphate	0·248	Inorg. P, mg./5 c.c.	0·013	0·020	0·026	0·034	0·040	0·047	0·051	0·059
		Dephosph., %	5·2	8·1	10·5	13·7	16·1	19·0	20·6	23·8

(iii) *Characteristics of salts.* This table is based on our observations and information taken from Levene and Tipson, Gulland and Hobday (*locc. cit.*), and Levene (*J. Biol. Chem.*, 1919, **40**, 395).

Characteristic.	3′-Phosphate.	5′-Phosphate.	2′-Phosphate.
(*a*) Pptn. of Pb salt	pH 6·8—7·0	Dil. ammonia	pH 6·8—7·0
(*b*) Solubility of Ba salt in cold water	Sparingly	Easily	Easily
(*c*) Brucine salt:			
(i) Form	Needles; $7H_2O$	Needles	Prisms; $4·5H_2O$
(ii) $[\alpha]_D$ in dry pyridine	$-55·0°$ (*c*, 1·00), $-55·9°$ (*c*, 1·06)	$-69·7°$ (*c*, 0·97), $-68·8°$ (*c*, 1·05)	$-76·1°$ (*c*, 0·96), $t = 17°$
(iii) Solubility:			
(*α*) Water	Sparingly sol., cold and hot	Mod. sol. cold, easily sol. hot	Sparingly sol. cold, 1 : 18 pts. hot
(*β*) 33% EtOH	Sparingly sol. cold, 1 : *ca.* 80 pts. hot	Mod. sol. cold, easily sol. hot	Mod. sol. cold, 1 : 8 pts. hot
(*γ*) Abs. EtOH	Sparingly sol. cold, and hot	Sparingly sol. cold, easily sol. hot	Sparingly sol. cold, mod. sol. hot
(iv) M. p.:	These are unsharp and conditions must be standardised. Salt was dried for 48 hours over P_2O_5 at 15 mm.; m. p. tube 1 mm. diam.; temp. rise 4°/min.		
(*α*) Placed in bath at 153°	Gradually swelled to opaque mass from 175° to 185°; had become transparent drops by 188—190°	Shrank at 159°; formed a transparent mass, 162—165°	Shrank to opaque mass from 161° to 174°; had become transparent drops by 177—180°
(*β*) Placed in bath at 12° below top of range	In at 183°. Shrank, effervesced, and swelled to opaque mass 185—187°; had become transparent drops by 195°	In at 153°; as above.	In at 168°. Shrank 171°, swelled to opaque mass 172—175°; had become transparent drops by 180°

It is a pleasure to record our gratitude to the Government Grant Committee of the Royal Society and to Imperial Chemical Industries Ltd. for assistance. Our thanks are also due to Mr. H. F. W. Taylor for carrying out the potentiometric titration, to Mr. D. T. Elmore for a sample of brucine uridylate, and to Mr. J. Still for micro-analyses and an adaptation of Kolthoff and Lingane's method for estimation of brucine (*J. Amer. Pharm. Assoc.*, 1934, **23**, 404).

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68. *Acid Catalysis in the Iodination of Phenol. Iodination by Acyl Hypoiodites.*

By B. S. PAINTER and F. G. SOPER.

Phenol, in aqueous solutions buffered by weak acid and salt, reacts with iodine at a rate which varies inversely with the hydrogen-ion concentration and with the square of the iodide-ion concentration. This is in harmony with an interaction of hypoiodous acid with un-ionised phenol or, alternatively, of positive iodine with phenoxide ions. In addition, the rate of iodination at constant pH increases linearly with the concentration of buffer acid and this catalytic effect varies inversely as the square of the hydrogen-ion concentration. This catalytic effect is explicable in terms of an interaction of acyl hypoiodites with phenoxide ions.

A KINETIC study of the *N*-chlorination of amides (Mauger and Soper, *J.*, 1946, 71) has indicated that, in addition to chlorination by the hypochlorite ion, certain amides are also *N*-chlorinated at a rate dependent on the product of the concentrations of hypochlorous acid and of the acid present as a component of the buffer. This has been interpreted as evidence of chlorination by acyl hypochlorites. Acyl hypoiodites might be anticipated to be the most

stable of the acyl hypohalogenites, and the re-examination of the iodination of phenol (Soper and Smith, *J.*, 1927, 2757) is therefore of interest in order to determine whether the kinetic effects observed in *N*-chlorination are paralleled by similar effects in *C*-iodination.

The mechanism of the iodination of phenols was investigated by Cofman (*J.*, 1919, **115**, 1040), who showed that in acid solution molecular iodine did not iodinate, whilst in alkaline solution the active iodine was equal to the concentration of hypoiodous acid calculated from the known kinetics of iodate formation (Skrabal, *Monatsh.*, 1911, **32**, 171). As in acid solution the phenol is almost exclusively un-ionised, whilst in alkaline solution the highly reactive phenoxide ions would be present with possible complicating effects, the reaction was further studied by Soper and Smith (*loc. cit.*), using phosphate-buffered solutions in the near-neutral range, where the iodine existed practically entirely in the form of the tri-iodide ion. With solutions containing iodide and phenol in excess with respect to the iodine concentration, the reaction was pseudo-unimolecular. The speed, given $V = k_1 \times$ iodine titre $= k_1[I_3^-]$, was found to be directly proportional to the phenol concentration and inversely proportional to the square of the iodide concentration. Since the concentration of free iodine will vary inversely with the first power of the iodide concentration, free iodine cannot be an iodinating agent even in the presence of the highly reactive phenoxide ions. Assuming that the pH is such that the phenol present is practically entirely in the un-ionised state, Table I shows the dependence of k_1 on the hydrogen-ion concentration of the solution according to possible mechanisms of iodination. Soper and Smith found that k_1 varied inversely with hydrogen-ion concentration more rapidly than its first power but less rapidly than its second power, and concluded that HOI reacts both with un-ionised phenol and with the phenoxide ion.

TABLE I.

Iodinating agent.	Phenolic agent.	k_1 proportional to :	Iodinating agent.	Phenolic agent.	k_1 proportional to :
HOI	PhOH	$[PhOH][I^-]^{-2}[H^+]^{-1}$	OI^-	PhO^-	$[PhOH][I^-]^{-2}[H^+]^{-2}$
HOI	PhO^-	$[PhOH][I^-]^{-2}[H^+]^{-2}$	I^+	PhOH	$[PhOH][I^-]^{-2}[H^+]^{0}$
OI^-	PhOH	$[PhOH][I^-]^{-2}[H^+]^{-2}$	I^+	PhO^-	$[PhOH][I^-]^{-2}[H^+]^{-1}$

The re-examination of the reaction has shown that at constant pH the rate of iodination is greatly affected by the concentration of the buffer, being approximately a linear function of the concentration of the buffer acid HA. Thus the unimolecular constant k_1 may be expressed by $k_1 = k_0 + k_{HA}[HA]$, *i.e.*,

$$v = k_0[PhOH][I_3^-] + k_{HA}[HA][PhOH][I_3^-]$$

The effect, at 25·0°, of acetic acid on the rate over the pH range 4·66—5·26 is shown in Fig. 1. The addition of potassium nitrate shows that the effect of increasing the buffer strength is not a salt effect. This is shown at pH 4·96 in the inset (Fig. 2). The values of k_0, obtained by extrapolating k_1 to zero acid concentration, and the slopes of the curve which measure k_{HA}, both vary with the pH of the solution. These values of k_0 and k_{HA} are given in Table II, k_0 varying inversely as the hydrogen-ion concentration and k_{HA} inversely as the square of this concentration.

TABLE II.

pH.	$10^5[H^+]$.	k_0.	$10^5k_0[H^+]$.	k_{HA}.	$10^{10}k_{HA}[H^+]^2$.
5·26	0·55	0·066	0·0363	3·575	1·09
5·055	0·88	0·0422	0·0372	1·42	1·10
4·96	1·10	0·0334	0·0368	0·875	1·06
4·66	2·20	0·0174	0·0383	0·220	1·07

Since the total reaction rate varies directly with the phenol concentration and inversely with the square of the iodide-ion concentration, k_0 varies as $[PhOH][H^+]^{-1}[I^-]^{-2}$ and (cf. Table I) indicates reaction between hypoiodous acid and un-ionised phenol or, alternatively, between positive iodine ions and phenoxide ions.

The term involving catalysis by acetic acid can be interpreted as showing reaction between acetyl hypoiodite and the phenoxide ion. Assuming that the concentration of the former is determined by the constant K of the equilibrium $AcOH + I_2 \rightleftarrows AcOI + H^+ + I^-$, and that the catalysed rate is given by $v = k_{cat.}[AcOI][PhO^-]$, then, neglecting activity coefficients

$$v = k_{cat.}\frac{K[AcOH][I_2]}{[H^+][I^-]} \cdot \frac{K_a[PhOH]}{[H^+]}$$

$$= k_{cat.}KK_{I_2}K_a\frac{[PhOH][I_3^-][AcOH]}{[H^+]^2[I^-]^2}$$

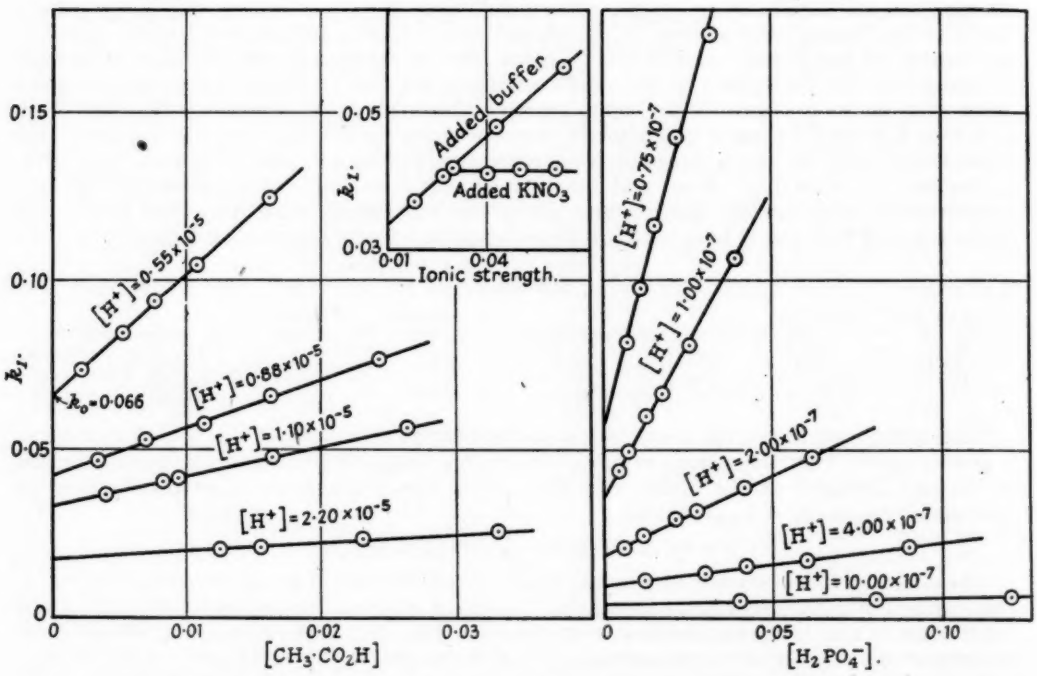
where K_{I_3} is the equilibrium constant of the reaction $I_3 = I_2 + I^-$ (Bray and McKay, *J. Amer. Chem. Soc.*, 1910, **32**, 914). Comparison with $v = k_1[I_3^-] = k_0[I_3^-] + k_{HA}[AcOH][I_3^-]$ gives

$$k_{HA} = k_{cat.}KK_{I_3}K_a[PhOH]/[H^+]^2[I^-]^2$$

showing the observed dependence on hydrogen- and iodide-ion concentrations. Other possible halogenating agents have been considered whose concentration would be proportional to the concentration of the acetic acid, but only acetyl hypoiodite fulfils the further required conditions of dependence of reaction rate on $[PhOH][H^+]^{-2}[I^-]^{-2}$.

Iodination in Phosphate Buffers.—A further test of the dependence of k_0 and k_{HA} on hydrogen-ion concentration was made in phosphate buffer solutions and the results obtained at 25·0°

FIG. 1. FIG. 2. FIG. 3.



are shown in Fig. 3. The values of k_0 and k_{HA} deduced from the curves are given in Table III and, as before, k_0 is found to be inversely proportional to the hydrogen-ion concentration and k_{HA} inversely proportional to its square.

TABLE III.

pH.	$10^7[H^+]$.	k_0.	$10^7k_0[H^+]$.	k_{HA}.	$10^{14}k_{HA}[H^+]^2$.
7·12	0·75	0·057	0·043	3·65	2·04
7·00	1·00	0·036	0·036	1·86	1·86
6·70	2·00	0·018	0·036	0·48	1·92
6·40	4·00	0·009	0·036	0·13	2·08
6·00	10·00	0·004	0·040	0·02	2·0

In phosphate buffers, the ion $H_2PO_4^-$ has replaced the free acid of the acetate buffers and the catalysed term can be explained in terms of an iodinating ion, iodine hydrogen phosphate, formed by $H_2PO_4^- + I_2 \rightleftarrows HIPO_4^- + H^+ + I^-$. Such an iodinating agent reacting with phenoxide ions gives the required dependence of k_{HA} on $[PhOH][I^-]^{-2}[H^+]^{-2}$. That the increased rate of reaction with increased phosphate buffer strength is not a salt effect was shown by increasing the ionic strength over a similar range with potassium nitrate, no appreciable alteration in k_1 being observed.

Comparison of the Catalytic Effects of Other Weak Acids.—Since the catalytic effect of the weak acid is dependent on the hydrogen-ion concentration of the solution, comparison of the

catalytic effects of dihydrogen phosphate, hydrogen maleate, hydrogen phthalate, and acetic acid was made at a constant pH of 6·0. This pH was chosen so as to minimise catalytic effects due to other acidic ions. The values obtained are given in Table IV.

TABLE IV.

$[PhOH] = 0{\cdot}0100$; $[I^-] = 0{\cdot}100$; $[I_2]$ added $= 0{\cdot}001$M.

	Dihydrogen phosphate.	Hydrogen maleate.	Hydrogen phthalate.	Acetic acid.
k_0	0·40	0·43	0·42	0·38
k_{HA}	0·017	0·072	0·88	1·41
$K_a \times 10^7$	0·597 *	2·6 *	39 *	186

* Second dissociation constants (see below).

In the cases of the first three acids the amounts of the un-ionised acids present at pH 6 will be negligible and the catalytic effects will be due to the ions $H_2PO_4^-$, $C_4H_2O_4{\cdot}H^-$, $C_8H_4O_4{\cdot}H^-$. Hence the second ionisation constants of these acids are used for purposes of comparison, and the values given are those recorded by Guggenheim and Schindler (*J. Physical Chem., Chem.*, 1934, **38**, 533), Chandler (*J. Amer. Chem. Soc.*, 1908, **30**, 713), Kuhn and Wassermann (*Helv. Chim. Acta*, 1928, **11**, 44), and Lundén (*Zentr.*, 1908, I, 787). The stronger the acid the greater its catalytic effect, and hence the disturbing effect in phosphate buffers due to the weakly acidic HPO_4^{--} ion will be slight. This relation of the strength of acid to its catalytic effect parallels the observed catalytic effects of acids (Mauger and Soper, *loc. cit.*) in the *N*-chlorination of *N*-methylacetamide. The relation may be due to increasing formation of the acyl hypoiodite with increase of acid strength. Alternatively, it may be due to the greater ease of release, at the point of substitution, of the iodine from the acyl hypoiodite in the form of positive iodine.

The kinetics of the iodination conform with either (*a*) or (*b*) :

$$v = k_0'[HOI][PhOH] + k'_{HA}[AcOI][PhO^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

$$v = k_0''[I^+][PhO^-] + k'_{HA}[AcOI][PhO^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

and other possible iodinating mechanisms appear to be eliminated. The uncatalysed reaction is explicable in terms either of positive iodine and phenoxide ions or of hypoiodous acid and un-ionised phenol. In mechanism (*a*) the hypoiodous acid attacks the un-ionised phenol in the uncatalysed reaction, but the acyl hypoiodite attacks only the phenoxide ion. Since the phenoxide ion is much more easily halogenated than un-ionised phenol (Soper and Smith, *J.*, 1926, 1582), hypoiodous acid must on this view be a more powerful iodinating agent than the acyl hypoiodite, for which some explanation is required.

In the iodination of phenol by different agents, two of the stages in the four-stage nuclear substitution process are the same, namely, the capture of the positive halogen and proton release by the carbon atom at the point of substitution. Ease of iodination by a series of iodinating agents is therefore governed by the other two stages, the ease of ionisation of the halogenating molecule into positive halogen and the ease of removal of the released proton by the residue of the halogenating molecule, the four processes blending and determining the energy of activation. If the ease of formation of positive halogen is a dominating factor, acyl hypoiodite should form a more effective iodinating agent than hypoiodous acid since nuclear release occurs more easily from the acetate ion than from the hydroxyl ion. But when hypoiodous acid iodinates, the released proton combines with hydroxyl to eliminate water whilst an acyl hypoiodite forms an acid from proton and acid ion. The much greater proton affinity of the hydroxyl ion than of the acetate ion may therefore dominate and so provide an explanation for mechanism (*a*). Interpretation (*b*), however, has formal simplicity, phenoxide ions reacting both with positive iodine in the uncatalysed reaction and with acyl hypoiodite in the acid-catalysed reaction. This simplification would receive some support by analogy with the chlorination of phenol by hypochlorous acid (Soper and Smith, *loc. cit.*) which also involves the phenoxide ions only.

EXPERIMENTAL.

Reaction mixtures were brought to thermal equilibrium at 25·0° ± 0·02°, and the reaction initiated by adding a solution of phenol to the buffered solution of iodine and iodide. Aliquot portions (10 c.c.) were examined by running them into 30 c.c. of N-sulphuric acid freed from oxygen by carbon dioxide,

and titrating against thiosulphate. Iodine and phenol in acid solution are stable, the iodine titre decreasing by less than 3% in 7 days. A typical run at pH 4·96 is shown below:

[PhOH] = 0·0100M; $[I^-]$ = 0·0100M; $[I_2]$ added = 0·0010M; [AcOH] = 0·00417M; [AcONa] = 0·00832M.

Time, mins.	0	8·6	12·3	14·39	17·0	20·2	25·2
$[I_2^-] \times 10^4$	9·38	6·95	5·97	5·62	5·02	4·60	3·66
$k_1 \times 10^3$	—	3·48	3·67	3·56	3·67	3·53	3·73

Points shown in Figs. 1, 2, and 3 represent the mean values obtained from duplicate experiments.

Buffer solutions were prepared from 0·2M-acid and 0·2M-sodium hydroxide, and the pH given in each case refers to a solution in which the sum of the concentrations of acid and acid ion is 0·05M. Acetate and phosphate buffers were prepared from the figures quoted by Clark ("Determination of Hydrogen Ions," 1928, pp. 219, 200), and phthalate buffer from figures quoted by Reilly and Rae ("Physico-Chemical Methods," 1940, Vol. II, 482). These were checked at the standard concentration by using a Cambridge glass electrode and found to be within 0·01 unit of pH in each case. Maleic acid buffer was prepared so as to give a pH of 6·00 using the glass electrode. All buffers were shown to be stable to iodine over an examined period of 2 days, and the phenol iodinations were examined over an average period of 2 hours.

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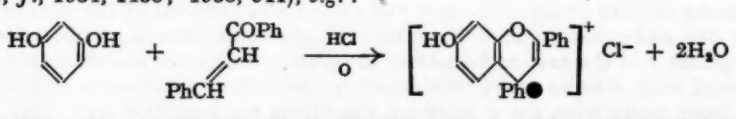
69. *A New Synthesis of Benzopyrylium Salts.*

By A. W. JOHNSON and R. R. MELHUISH.

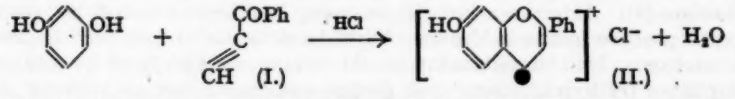
Benzopyrylium salts including flavylium salts and some pyrylium salts are synthesised by a new reaction which consists of the interaction of phenols with ethynyl ketones in the presence of acids. The general nature of the reaction is illustrated by the use of resorcinol, *m*-methoxyphenol, pyrogallol, phloroglucinol, β-naphthol, 2-hydroxycarbazole, 6-ethoxythioindoxyl, phenol, *p*-cresol, and *p*-methoxyphenol with phenyl ethynyl ketone, *m*-methoxyphenyl ethynyl ketone, and methyl ethynyl ketone.

THE condensation reactions of β-diketo-compounds, R·CO·CH_2·COR′, involving both of the keto-groups with the elimination of water can often be carried out equally well with the αβ-acetylenic carbonyl compounds, R·CO·C:CR′ (or R·C:C·COR′). Thus, these compounds with hydrazines give pyrazole derivatives, with hydroxylamine give *iso*oxazole derivatives, and with amidines, guanidines, or urea give pyrimidines. β-Keto-acids and their derivatives often behave similarly to the corresponding αβ-acetylenic acids. Also, the αβ-acetylenic compounds can be employed in reactions which are normally carried out with the corresponding ethylenic compounds in the presence of an oxidising agent, *e.g.*, many of the well-known quinoline syntheses. Thus, by analogy, further reactions of the αβ-acetylenic compounds can often be predicted.

Benzopyrylium salts (Hill, *Chem. Reviews*, 1936, **19**, 27) have been obtained by the condensation of β-diketones or β-keto-aldehydes with reactive phenols (von Bülow *et al.*, *Ber.*, 1901, **34**, 1189, 1782, 2368, 3889, 3916; Hill, *loc. cit.*) and by the condensation of αβ-ethylenic ketones with reactive phenols in the presence of an oxidising agent such as chloranil (Robinson and Walker, *J.*, 1934, 1435; 1935, 941), *e.g.*:



It therefore appeared probable that benzopyrylium salts would be obtained from the reaction of αβ-ethynyl ketones and phenols in the presence of acids; *e.g.*, resorcinol and phenyl ethynyl ketone (I) should yield 7-hydroxyflavylium (7-hydroxy-2-phenylbenzopyrylium) (II) salts:

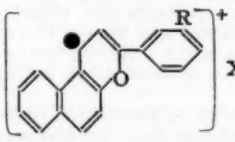
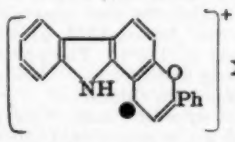


The probability that benzopyrylium salts would be obtained in this way was supported by an observation by Kalff (*Rec. Trav. chim.*, 1927, **46**, 594) who mentioned that the reaction of phenylpropiolic aldehyde with resorcinol in ethereal or glacial acetic acid solution in the presence of a trace of hydrogen chloride gave a bright red solution, although he did not identify any product.

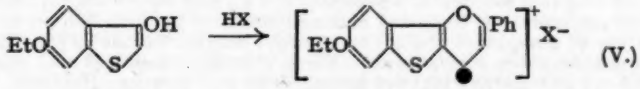
This probability has now been examined experimentally and as a result a useful method for the production of benzopyrylium salts has been elaborated.

αβ-Ethynyl ketones (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) have been brought into reaction with phenols in ethereal or preferably glacial acetic acid solution in the presence of mineral acids to give benzopyrylium salts in excellent yields (flavylium salts were obtained from aryl ethynyl ketones and monocyclic phenols). In the early experiments hydrogen chloride was used as the mineral acid, but it was later found that the use of concentrated sulphuric acid was more convenient. In the procedure usually adopted the reactants were dissolved in glacial acetic acid and sulphuric acid was added; after 24 hours the crystalline benzopyrylium sulphate had usually separated but, if not, it was precipitated by the addition of dry ether. The sulphate could be converted into the chloride by crystallisation from dilute hydrochloric acid. Perchlorates and ferrichlorides were prepared from the chlorides for analytical purposes, since these salts give better analyses than the chlorides and more commonly have characteristic melting points.

The phenolic component was first shown to be variable within the usual limits of the term " reactive " phenol, and benzopyrylium salts have been obtained by the reaction of phenyl ethynyl ketone and the following phenols: resorcinol, *m*-methoxyphenol, pyrogallol, and phloroglucinol, to give 7-hydroxy-, 7-methoxy-, 7 : 8-*dihydroxy*- and 5 : 7-dihydroxy-flavylium salts, and with β-naphthol and 2-hydroxycarbazole to give 2-phenyl-β-naphthopyrylium (III; R = H) and 2-*phenylcarbazolo*(1′ : 2′ : 5 : 6)*pyrylium* (IV) salts respectively.

(III.)  (IV.) 

The interaction of phloroglucinol and phenyl ethynyl ketone is undoubtedly the most convenient method of synthesising 5 : 7-dihydroxyflavylium (chrysinidin) salts yet described. m-*Methoxyphenyl ethynyl ketone* and β-naphthol reacted to give 2-(3′-*methoxyphenyl*)-β-*naphthopyrylium* (III; R = OMe) salts, and methyl ethynyl ketone and β-naphthol reacted to give 2-methyl-β-naphthopyrylium salts. 6-Ethoxythioindoxyl reacted with phenyl ethynyl ketone in the presence of acids to give 2-*phenyl*-6′-*ethoxythionaphtheno*(2′ : 3′ : 5 : 6)*pyrylium* (V) salts, the 6-ethoxythioindoxyl presumably reacting in the enol form (VI):

(VI.)  (V.)

No pyrylium salts have been isolated, when using the reaction conditions described, from phenyl ethynyl ketone and phenol, *m*-cresol, or thio-*p*-cresol, nor was there any reaction with the following " active " methylene compounds: 1-phenyl-3-methyl-5-pyrazolone, *N*-propyloxindole, 1 : 3-dihydroxy*iso*quinoline, 1 : 3-diketohydrindene, or 7-chloro-3-keto-5-methyl-2 : 3-dihydro-1 : 4-benzthiazine. Immediate deep red colourations were obtained in the reactions of phenyl ethynyl ketone with quinol, *m*-diethylaminophenol, and α-naphthol in acetic acid in the presence of sulphuric acid, although no products were isolated.

Although flavylium chloride itself cannot be prepared by the reaction of salicylaldehyde and acetophenone in the presence of hydrogen chloride, flavylium perchlorate can readily be prepared from these reactants in the presence of perchloric acid (Löwenbein and Rosenbaum, *Annalen*, 1926, **448**, 242). Similarly, benzopyrylium salts have been obtained from some apparently inoperable phenols by effecting the reaction with perchloric acid or with a solution of ferric chloride in hydrochloric acid as the condensing system. Thus, phenol and phenyl ethynyl ketone in the presence of a solution of ferric chloride in hydrochloric acid slowly reacted to give flavylium ferrichloride. The yield of flavylium ferrichloride was poor, possibly owing to simultaneous *p*-substitution of the phenol, since from *p*-cresol under similar conditions a high yield of 6-*methylflavylium ferrichloride* was rapidly obtained. It has also been shown that *p*-methoxyphenol and phenyl ethynyl ketone in the presence of acids give 6-methoxyflavylium salts. These later results show that the new reaction of ethynyl ketones can be used with phenols other than " reactive " phenols.

In order to demonstrate the identity of the benzopyrylium salts obtained by the new reaction, a number have been compared with the products of condensation of the appropriate

o-hydroxy-aldehyde and acetophenone by the conventional method (Perkin, Robinson, and Turner, *J.*, 1908, **93**, 1085; Hill, *loc. cit.*) [*e.g.*, 2 : 4-dihydroxybenzaldehyde and acetophenone in the presence of hydrogen chloride give (II)]. Identity has thus been established for the 7-hydroxy-, 7 : 8-dihydroxy-, and 6- and 7-methoxy-flavylium salts and for the 2-phenyl-β-naphthopyrylium salts.

All the benzopyrylium salts from the ethynyl ketones were pure compounds usually obtained in high yields, and there were no indications of the formation of mixtures of salts, such as are often formed by the von Bülow method (Hill, *loc. cit.*) or may be formed by the Perkin method (Hill and Melhuish, *J.*, 1935, 88). The new method cannot be used for the synthesis of 3-substituted flavylium salts, however, which include most of the naturally occurring anthocyanins.

Experimental.

M. p.'s are uncorrected. In all crystallisations of benzopyrylium salts, the suspension of the salts in the solvent was heated slowly, preferably on the steam-bath, as many of the salts were easily decomposed by heat.

The "ferric chloride solution" referred to throughout this paper was prepared by dissolving anhydrous ferric chloride (100 g.) in concentrated hydrochloric acid (150 c.c.).

2-*Phenyl-β-naphthopyrylium Chloride.*—(*a*) Dry hydrogen chloride was passed into a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in acetic acid (10 c.c.) for 1 hour and the mixture left overnight. 2-Phenyl-β-naphthopyrylium chloride (0·8 g.) separated as long orange needles and was crystallised from 3% hydrochloric acid. The product had m. p. 133—134° alone and mixed with an authentic specimen prepared by the condensation of 2-hydroxy-1-naphthaldehyde and acetophenone in the presence of hydrogen chloride (Kondo and Segawa, *J. Pharm. Soc. Japan*, 1931, **51**, 859, give m. p. 135°; Russell and Speck, *J. Amer. Chem. Soc.*, 1941, **63**, 851, give m. p. 118°). The product dissolved in concentrated sulphuric acid to give a yellow solution with a strong fluorescence. A flocculent red precipitate was obtained on addition of alkali to an aqueous solution of the chloride.

(*b*) Concentrated sulphuric acid (1 c.c.) was added to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). The solution became deep red and a crystalline solid separated after 1 minute. Next day, the solid was separated and crystallised from 3% hydrochloric acid (75 c.c.). A further quantity was obtained from the acetic acid mother liquors by dilution with dry ether (30 c.c.). 2-Phenyl-β-naphthopyrylium chloride (1·1 g.), m. p. 132—133°, was obtained as orange needles. The ferrichloride formed orange-red needles from acetic acid, m. p. 188° alone and mixed with an authentic specimen (Decker and Fellenberg, *Annalen*, 1907, **364**, 42, give m. p. 187·5°). The *perchlorate* formed orange needles from acetic acid, m. p. 245° alone and mixed with a specimen prepared from authentic 2-phenyl-β-naphthopyrylium chloride (Found: C, 63·8; H, 3·9; Cl, 9·8. $C_{19}H_{13}O_5Cl$ requires C, 63·95; H, 3·65; Cl, 9·95%).

(*c*) 2-Phenyl-β-naphthopyrylium ferrichloride (1·4 g.) was also obtained by the addition of ferric chloride solution (5 c.c.) to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The perchlorate (1·0 g.) was obtained similarly by the addition of 70% perchloric acid (1 c.c.) to a solution of β-naphthol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.).

2-*Methyl-β-naphthopyrylium Ferrichloride.*—Ferric chloride solution (3 c.c.) was added to a solution of β-naphthol (0·5 g.) and methyl ethynyl ketone (0·25 g.; Bowden, Heilbron, Jones, and Weedon, *loc. cit.*) in acetic acid (5 c.c.). A crystalline solid was rapidly formed, and next day the solid was separated and crystallised from acetic acid. The *ferrichloride* was thus obtained as pale green needles (0·75 g.), m. p. 141—143° (Found: Cl, 35·7. $C_{14}H_{11}OCl_4Fe$ requires Cl, 36·1%).

m-*Methoxyphenylethynylcarbinol.*—Purified acetylene was rapidly passed into liquid ammonia (1000 c.c.) with stirring and cooling, and sodium (17 g.) added in small pieces in such a manner that the blue colour never persisted for more than a few seconds. A solution of *m*-methoxybenzaldehyde (92 g.) in ether (100 c.c.) was then added during 1 hour and the mixture was stirred and cooled for a further 3 hours with continued passage of acetylene. The ammonia was allowed to evaporate overnight, and ether and cold dilute hydrochloric acid were added to the residue with stirring. The ethereal layer was separated and repeatedly washed with sodium hydrogen carbonate solution in order to remove the *m*-methoxybenzoic acid formed by the simultaneous Cannizzaro reaction. The solution was dried and the ether removed; fractionation of the residue gave the *carbinol* as a pale yellow oil, b. p. 103°/3 mm. (Found: C, 73·8; H, 6·0. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%). The carbinol readily gave a white insoluble silver derivative with ammoniacal silver nitrate.

m-*Methoxyphenyl Ethynyl Ketone.*—To a stirred solution of *m*-methoxyphenylethynylcarbinol (38 g.) in acetone (50 c.c.) a solution of chromium trioxide (21 g.) in water (67 c.c.) and concentrated sulphuric acid (18 c.c.) was slowly added in an atmosphere of nitrogen. The addition lasted one hour and the temperature of the reaction mixture was kept at 10—15° by external cooling. After being stirred for a further 30 minutes the mixture was diluted with water and the product extracted with ether. Evaporation of the ether gave a dark yellow oil which was distilled to give the *ketone* as a pale yellow oil, b. p. 92—93°/1 mm., which solidified on cooling and was crystallised from light petroleum (b. p. 60—80°); it then had m. p. 15—16° (Found: C, 74·8; H, 4·9. $C_{10}H_8O_2$ requires C, 75·0; H, 5·0%).

2-m-*Methoxyphenyl-β-naphthopyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of β-naphthol (0·5 g.) and *m*-methoxyphenyl ethynyl ketone (0·55 g.) in acetic acid (10 c.c.). After 2 days the deep red solution was diluted with ether and the precipitated salt crystallised from dilute hydrochloric acid (80 c.c.). It was thus obtained as small red prisms, m. p. 124—125° (1·03 g.). The *ferrichloride*, m. p. 178—179°, formed orange needles from acetic acid (Found: C, 49·35; H, 3·3; Cl, 29·15. $C_{20}H_{15}O_2Cl_4Fe$ requires C, 49·5; H, 3·1; Cl, 29·3%). The *perchlorate*, m. p. 210—211°, formed

small brown needles from acetic acid (Found : C, 62·1; H, 4·0; Cl, 9·2. $C_{20}H_{15}O_6Cl$ requires C, 62·1; H, 3·9; Cl, 9·2%). The ferrichloride (1·05 g.) and perchlorate (1·05 g.) were also obtained from the reaction of β-naphthol (0·5 g.) and *m*-methoxyphenyl ethynyl ketone (0·55 g.) in the presence of ferric chloride solution (3 c.c.) or 70% perchloric acid (1 c.c.) respectively.

7 : 8-*Dihydroxyflavylium Chloride.*—(*a*) Concentrated sulphuric acid (5 c.c.) was added to a solution of 2 : 3 : 4-trihydroxybenzaldehyde (1·54 g.) and acetophenone (1·2 g.) in acetic acid (20 c.c.). Crystals slowly separated from the dark red solution, and next day the whole was poured into dry ether. The deep purple-red salt which separated was washed with ether, collected (2·35 g.), and crystallised by dissolving in hot 3% hydrochloric acid (500 c.c.) and then adding concentrated hydrochloric acid (85 c.c.). The salt (1·65 g.) crystallised slowly as permanganate-coloured rods, m. p. 236—237° (decomp.). Its alcoholic solution acquired a deep blue colouration on the addition of sodium carbonate solution. The *perchlorate*, m. p. 223—224°, formed dark reddish-brown prisms from acetic acid (Found : C, 53·1; H, 3·35; Cl, 10·8. $C_{15}H_{11}O_7Cl$ requires C, 53·2; H, 3·25; Cl, 10·5%).

(*b*) Concentrated sulphuric acid (0·5 c.c.) was added to a solution of pyrogallol (0·3 g.) and phenyl ethynyl ketone (0·3 g.) in acetic acid (5 c.c.). The dark red solution solidified almost completely after 1 hour at room temperature. Next day, the solid was crystallised as in the previous experiment to yield 7 : 8-dihydroxyflavylium chloride (0·5 g.), m. p. 236—237° (decomp.). The corresponding perchlorate had m. p. 223—224° alone and mixed with the specimen obtained in the previous condensation.

5 : 7-*Dihydroxyflavylium Chloride* (*Chrysinidin Chloride*).—Concentrated sulphuric acid (1·0 c.c.) was added to a solution of phloroglucinol (1·0 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). A deep red colouration was produced and a red precipitate formed almost immediately. Next day, the precipitate was separated and extracted with 0·5% hydrochloric acid (3 × 250 c.c.); 5 : 7-dihydroxyflavylium chloride was thus obtained as small red needles (0·8 g.), m. p. > 250° (cf. Pratt, Robertson, and Robinson, *J.*, 1927, 1975). A considerable amount of insoluble red material remained after this extraction. The corresponding perchlorate formed reddish-brown platelets from acetic acid, m. p. 243—244° (Pratt, Robertson, and Robinson, *loc. cit.*, give m. p. 244°).

7-*Hydroxyflavylium Chloride.*—Concentrated sulphuric acid (1·0 c.c.) was added to a solution of resorcinol (0·9 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). The dark red solution was kept at room temperature for 4 days after which time a considerable amount of crystalline material had formed. This was separated and a further amount obtained by the addition of dry ether (50 c.c.) to the filtrate. The combined solids were recrystallised from 7% hydrochloric acid, and 7-hydroxyflavylium chloride was thus obtained as red-brown needles, m. p. > 260° (Perkin, Robinson, and Turner, *loc. cit.*, say the m. p. is indefinite. The value given by Bülow and Sicherer, *Ber.*, 1901, **34**, 3889, m. p. 152—153°, has not been confirmed by later workers). The corresponding *ferrichloride* was obtained as orange-red needles and, after crystallisation from acetic acid, had m. p. 166—167°; it caused sneezing, and was stable in air (Found : C, 42·95; H, 2·7; Cl, 33·7. $C_{15}H_{11}O_2Cl_4Fe$ requires C, 42·65; H, 2·85; Cl, 33·65%). The *perchlorate*, m. p. 220—221°, alone and mixed with a specimen prepared from authentic 7-hydroxyflavylium chloride, formed orange plates from acetic acid (Found : C, 55·8; H, 3·7; Cl, 10·85. $C_{15}H_{11}O_6Cl$ requires C, 55·64; H, 3·7; Cl, 10·95%).

7-*Methoxyflavylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of *m*-methoxyphenol (1·0 g.) and phenyl ethynyl ketone (1·0 g.) in acetic acid (10 c.c.). The deep red solution was kept at room temperature for two days, and the product was precipitated by the addition of dry ether (100 c.c.). The solid was separated and crystallised from 7% hydrochloric acid; 7-methoxyflavylium chloride was thus obtained as deep orange needles, m. p. 96—97° (Robinson and Crabtree, *J.*, 1918, **113**, 877, give m. p. 102—103°; Row and Seshadri, *Proc. Indian Acad. Sci.*, 1941, **13**, *A*, 510, give m. p. 105—106°). The yellow solution of the chloride in dilute hydrochloric acid showed a bright green fluorescence. The corresponding ferrichloride formed golden-brown needles from acetic acid, m. p. 150—151°; mixed m. p. with an authentic specimen, 149—150° (Hill, *J.*, 1935, 85, gives m. p. 147°). The *perchlorate*, m. p. 222—223°, alone and mixed with a specimen prepared from authentic chloride, formed pale yellow plates from acetic acid in which it dissolves with a deep green fluorescence (Found : C, 57·0; H, 4·4; Cl, 10·85. $C_{16}H_{12}O_6Cl$ requires C, 56·7; H, 4·15; Cl, 10·75%).

2-*Phenylcarbazolo*(1′ : 2′ : 5 : 6)*pyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of 2-hydroxycarbazole (0·6 g.; m. p. 272—273°) and phenyl ethynyl ketone (0·4 g.) in acetic acid (40 c.c.). A solid was rapidly precipitated from the dark red solution. After 2 days at room temperature, dry ether (100 c.c.) was added to the mixture and the solid separated and crystallised from 3% hydrochloric acid (2,500 c.c.). The chloride (0·7 g.) was obtained as a dark brown crystalline product which did not melt below 270°. The *ferrichloride* formed small dark red crystals, m. p. 235—236°, from acetic acid (Found : C, 50·6; H, 2·95. $C_{21}H_{14}ONCl_4Fe$ requires C, 51·0; H, 2·8%). The *perchlorate* formed black micro-crystals with a metallic lustre, m. p. 267—268°, from acetic acid (Found : C, 63·4; H, 3·2. $C_{21}H_{14}O_6NCl$ requires C, 63·7; H, 3·5%).

2-*Phenyl*-6′-*ethoxythionaphtheno*(2′ : 3′ : 5 : 6)*pyrylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of 6-ethoxythioindoxyl (0·75 g.; m. p. 122°) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). The dark red solution was kept overnight and then, after the addition of dry ether (100 c.c.), the precipitate was separated and crystallised from 3% hydrochloric acid. The chloride was thus obtained as a pale brown amorphous solid which was very susceptible to heat. The *ferrichloride* formed red needles, m. p. 170—171°, from acetic acid (Found : C, 44·7; H, 2·7; Cl, 28·1. $C_{19}H_{13}O_2Cl_4SFe$ requires C, 45·1; H, 3·0; Cl, 28·1%). The *perchlorate* formed small brown prisms, m. p. 231—233°, from acetic acid (Found : C, 56·2; H, 3·1. $C_{19}H_{13}O_6ClS$ requires C, 56·1; H, 2·7%).

6-*Methylflavylium Ferrichloride.*—Ferric chloride solution (3 c.c.) was added to a solution of *p*-cresol (0·4 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The dark yellow solution soon deposited a crystalline product. Next day this was separated and crystallised from acetic acid; 6-*methylflavylium ferrichloride* (0·7 g.) was thus obtained as long yellow needles, m. p. 171—172° (Found : C, 46·2; H, 3·4; Cl, 34·0. $C_{16}H_{13}OCl_4Fe$ requires C, 45·8; H, 3·1; Cl, 33·9%).

6-*Methoxyflavylium Chloride.*—Concentrated sulphuric acid (1 c.c.) was added to a solution of *p*-methoxyphenol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (10 c.c.). No precipitate

separated from the dark brown solution after 2 days at room temperature. The flavylium salt was precipitated with dry ether (30 c.c.) and crystallised from 7% hydrochloric acid; 6-methoxyflavylium chloride (0·5 g.) was thus obtained as dark brown needles, m. p. 95—96° (Irvine and Robinson, *J.*, 1927, 2086, give m. p. 97°). The corresponding ferrichloride, m. p. 202—203° (Irvine and Robinson, *loc. cit.*, give m. p. 203°), formed brown platelets from acetic acid. The ferrichloride (1·1 g.) was also obtained by the addition of ferric chloride solution (3 c.c.) to a solution of *p*-methoxyphenol (0·5 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). The precipitated product was separated and crystallised from acetic acid.

Flavylium Ferrichloride.—Ferric chloride solution (3 c.c.) was added to a solution of phenol (0·35 g.) and phenyl ethynyl ketone (0·5 g.) in acetic acid (5 c.c.). After 3 days at room temperature the crystalline product (0·1 g.) was separated and crystallised from acetic acid; flavylium ferrichloride was thus obtained as long yellow needles, m. p. 138—139° (Hill *et al.*, *J.*, 1935, 85; 1937, 41, give m. p. 140°).

The authors are indebted to Mr. J. D. Rose for his interest in the work.

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70. *The Nitration of* 1 : 5-*Dihydroxy- and* 1 : 5-*Diacetoxy-naphthalene,* 1-*Acetoxy*-5-*methoxynaphthalene,* 5-*Methoxy*-1-*naphthol, and* 1 : 5-*Dimethoxynaphthalene.*

By R. H. THOMSON, E. RACE, and (the late) F. M. ROWE.

Nitration of the compounds named in the title has been studied. Oxidation to a methoxynaphthaquinone or to a nitromethoxyphthalic acid, or conversion into and comparison with a bromo-compound, has enabled the products to be orientated. Thus, the 2 : 6-*dinitro-* and 2 : 4 : 6 : 8-*tetranitro*-derivatives are obtained from 1 : 5-dihydroxynaphthalene; the 2 : 4-*dinitro-* and 2 : 4 : 6-*trinitro*-5-*acetoxy*-1-*naphthols* from 1 : 5-diacetoxynaphthalene; the 2 : 4-*dinitro*-derivative from 5-methoxy-1-naphthol; 8-*nitro-* and 6 : 8-*dinitro*-derivatives and 2 : 8-*dinitro*-5-*methoxy*-1-*naphthol* from 1-acetoxy-5-methoxynaphthalene; and 4-*nitro-*, 4 : 8-*dinitro-*, 2 : 4 : 8-*trinitro-*, and 2 : 4 : 6 : 8-*tetranitro*-derivatives from 1 : 5-dimethoxynaphthalene.

BENTLEY, ROBINSON, and WEIZMANN (*J.*, 1907, **91**, 104) prepared mono- and di-nitro-derivatives of 1 : 5-dimethoxynaphthalene, but did not determine their constitutions. We have now orientated the former by reduction and conversion of the amino-compound into a bromo-1 : 5-dimethoxynaphthalene, different from 2-bromo-1 : 5-dimethoxynaphthalene (Carter, Race, and Rowe, *J.*, 1942, 236), but identical with the product obtained by Fischer and Bauer (*J. pr. Chem.*, 1916, **94**, 15) by direct monobromination of 1 : 5-dimethoxynaphthalene. Since 1 : 5-dimethoxynaphthalene is converted by dibromination into 4 : 8-dibromo-1 : 5-dimethoxynaphthalene (Carter, Race, and Rowe, *loc. cit.*,) the monobromo-compound must be 4-*bromo*-1 : 5-*dimethoxynaphthalene*. Further, reduction of nitro-1 : 5-dimethoxynaphthalene and oxidation of the amino-1 : 5-dimethoxynaphthalene with chromic acid resulted in elimination of the methoxyl group in the *p*-position to the amino-group with formation of 5-*methoxy*-1 : 4-*naphthaquinone*, a product which cannot be prepared directly from 5-hydroxy-1 : 4-naphthaquinone (juglone) by methylation. Thus, the mononitro-derivative of 1 : 5-dimethoxynaphthalene is 4-*nitro*-1 : 5-*dimethoxynaphthalene* (I), which was also obtained by mononitration of 1-acetoxy-5-methoxynaphthalene, followed by hydrolysis and methylation. Reduction of the mononitro-1-acetoxy-5-methoxynaphthalene (VII) and oxidation of the product with chromic acid did not give a quinone, indicating that the amino- and the acetoxy-group are in different rings in the naphthalene nucleus, and this was confirmed by further nitration to 6 : 8-*dinitro*-1-*acetoxy*-5-*methoxynaphthalene* (XI). Hence mononitration of 1-acetoxy-5-methoxynaphthalene, followed by hydrolysis of the product, gave 8-*nitro*-5-*methoxy*-1-*naphthol* (VIII).

Nitration of 1 : 5-diacetoxynaphthalene gave a dinitro-acetoxynaphthol, which, when hydrolysed and methylated, afforded a dinitro-1 : 5-dimethoxynaphthalene, m.p. 153° (VI), also obtained from 5-methoxy-1-naphthol by nitration with diacetyl orthonitric acid followed by methylation, as well as by further nitration of (VII) with diacetyl orthonitric acid followed by hydrolysis and methylation. One nitro-group is therefore in the *p*-position to a methoxyl group, and, since oxidation of the dinitroacetoxynaphthol with dilute nitric acid gave 4 : 6-*dinitro*-3-*hydroxyphthalic acid*, both nitro-groups must be in the same ring in the naphthalene nucleus. Thus, nitration of 1 : 5-diacetoxynaphthalene gave 2 : 4-*dinitro*-5-*acetoxy*-1-*naphthol* (XIV), as shown by the fact that this was converted by methylation into 6 : 8-*dinitro*-1-*acetoxy*-

5-methoxynaphthalene (XI), identical with the product afforded by nitration of (VII) with diacetyl orthonitric acid. Hydrolysis of (XI) with dilute sodium hydroxide solution gave 2 : 4-*dinitro*-1 : 5-*dihydroxynaphthalene* (XII) with elimination of both the acetyl and the methoxyl group, whilst boiling (XI) with water hydrolysed the methoxyl group with formation of 2 : 4-*dinitro*-5-*acetoxy*-1-*naphthol*, whereas boiling (XI) with methyl-alcoholic ammonia solution removed the acetyl group with formation of 6 : 8-*dinitro*-5-*methoxy*-1-*naphthol* (XIII), m. p. 202—204°, which was not identical with 2 : 4-*dintro*-5-*methoxy*-1-*naphthol* (V), m. p. 173° (decomp.), prepared by nitration of 5-methoxy-1-naphthol. Thus, in the nitration of 5-methoxy-1-naphthol, both nitro-groups enter the ring of the naphthalene nucleus which contains the hydroxyl group, whereas in the nitration of 1-acetoxy-5-methoxynaphthalene, both nitro-groups enter the ring containing the methoxyl group, as would be anticipated from electronic considerations. The dinitromethoxy-1-naphthols and some other methoxy-derivatives in this series resisted demethylation and gave consistently low results in methoxyl determinations.

The great lability of substituents in the α-position in 2 : 4-dinitro-compounds, indicated by the hydrolysis of the methoxyl group in 6 : 8-dinitro-1-acetoxy-5-methoxynaphthalene by boiling with water, was further illustrated by the ease with which a methoxyl group in 2 : 4-dinitro-1 : 5-dimethoxynaphthalene was replaced by an amino-group by reaction with ammonia in boiling alcoholic solution, forming 2 : 4-*dinitro*-5-*methoxy*-1-*naphthylamine*. Moreover, an attempted monoreduction of 2 : 4-dinitro-1 : 5-dimethoxynaphthalene with aqueous sodium sulphide gave 2 : 4-dinitro-5-methoxy-1-naphthol.

1 : 5-Dimethoxynaphthalene on nitration gives a dinitrodimethoxynaphthalene, m. p. 275°, converted by oxidation with dilute nitric acid into 6-nitro-3-methoxyphthalic acid, so the nitro-groups are in different rings in the naphthalene nucleus. In view of the *p*-directing influence of the methoxyl groups it is to be expected that the second nitro-group would enter the nucleus in position 8 to form a symmetrical compound (cf. dibromination of 1 : 5-dimethoxynaphthalene; Carter, Race, and Rowe, *loc. cit.*). This was supported by the isolation of this dinitro-compound as the sole product of dinitration of 1 : 5-dimethoxynaphthalene, by formation of 6-nitro-3-methoxyphthalic acid on oxidation, and by the general stability of the compound, particularly its failure to react with ammonia when heated in a sealed tube at 200°. Thus, dinitration of 1 : 5-dimethoxynaphthalene gave 4 : 8-*dinitro*-1 : 5-*dimethoxynaphthalene* (II).

1-Acetoxy-5-methoxynaphthalene is converted by nitric acid at 0° into a dinitro-5-methoxy-1-naphthol, m. p. 183° (gas evolution) (IX), different from (V) and (XIII), and (IX) was also obtained from 8-nitro-1-acetoxy-5-methoxynaphthalene (VII) by the action of nitric acid at 5°. Methylation of (IX) gave a dinitro-1 : 5-dimethoxynaphthalene (X), m. p. 135°. Since compound (X), which is the third dinitrodimethoxynaphthalene containing a nitro-group in position 4, is not identical with (II) or (VI), it must be 2 : 8-*dinitro*-1 : 5-*dimethoxynaphthalene*, and (IX) is 2 : 8-*dinitro*-5-*methoxynaphthol*.

Nitration of 1 : 5-dihydroxynaphthalene with copper nitrate in acetic anhydride gave a dinitrodihydroxynaphthalene (XX), not identical with (XII), and converted by methylation into a dinitro-1 : 5-dimethoxynaphthalene, m. p. 222° (XXI). Since this compound is not identical with any of the dinitro-1 : 5-dimethoxynaphthalenes (II), (VI), or (X) already described, it must be 2 : 6-*dinitro*-1 : 5-*dimethoxynaphthalene*, and its formation is analogous to the dibromination of 1 : 5-dihydroxynaphthalene (Carter, Race, and Rowe, *loc. cit.*).

Further nitration of 2 : 4-dinitro-1 : 5-dimethoxynaphthalene (VI) and of 4 : 8-dinitro-1 : 5-dimethoxynaphthalene (II) gave the same trinitro-derivative, which is therefore 2 : 4 : 8-*trinitro*-1 : 5-*dimethoxynaphthalene* (III).

1 : 5-Diacetoxynaphthalene with nitric acid at 50° gave a trinitro-5-acetoxy-1-naphthol, converted by hydrolysis and methylation into trinitro-1 : 5-dimethoxynaphthalene, m. p. 238° (XVII), which was not identical with (III) and so is 2 : 4 : 6-*trinitro*-1 : 5-*dimethoxynaphthalene*.

Finally, nitration of 2 : 4 : 8-trinitro-1 : 5-dimethoxynaphthalene gave a tetranitro-derivative, which was also obtained by nitrating 1 : 5-dihydroxynaphthalene with diacetyl orthonitric acid, followed by methylation of the product, and this compound is 2 : 4 : 6 : 8-*tetranitro*-1 : 5-*dimethoxynaphthalene* (IV).

Experimental.

(Where identity is specified, this was established by mixed m. p.)

4-*Nitro*-1 : 5-*dimethoxynaphthalene* (I) (Bentley, Robinson, and Weizmann, *J.*, 1907, **91**, 107).—Nitric acid (*d* 1·42, 4 c.c.) in acetic acid (4 c.c.) was added slowly to a stirred suspension of 1 : 5-dimethoxynaphthalene (10 g.) in acetic acid (400 c.c.) at room temperature. After 30 mins., the mixture was

warmed to 80° until complete dissolution was obtained, and then allowed to cool. 4-*Nitro*-1 : 5-*dimethoxynaphthalene* crystallised from acetic acid in yellow rhombic plates, m. p. 167° (11 g.; 89%) (Found: C, 62·1; H, 4·6; N, 6·1. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%).

4 : 8-*Dinitro*-1 : 5-*dimethoxynaphthalene* (II).—Twice as much nitric acid was used as in the preparation of (I) and the suspension was boiled. 4 : 8-*Dinitro*-1 : 5-*dimethoxynaphthalene* separated from acetic acid in pale yellow prismatic needles, m. p. 275°, which darkened on prolonged exposure to light (12·5 g.; 84%) (Found: C, 52·1; H, 3·55; N, 10·2. $C_{12}H_{10}O_6N_2$ requires C, 51·8; H, 3·9; N, 10·1%).

2 : 4 : 8-*Trinitro*-1 : 5-*dimethoxynaphthalene* (III).—Nitric acid (*d* 1·5, 15 c.c.) was added to a solution of compound (II) (2 g.) in boiling acetic acid (150 c.c.). After being refluxed for 1 hr., the solution was cooled and poured into water. The precipitate of 2 : 4 : 8-*trinitro*-1 : 5-*dimethoxynaphthalene* crystallised from dilute acetic acid in long yellow needles, m. p. 180° (1 g.; 43%) (Found: C, 44·7; H, 3·0; N, 12·8. $C_{12}H_9O_8N_3$ requires C, 44·6; H, 2·8; N, 13·0%).

2 : 4 : 6 : 8-*Tetranitro*-1 : 5-*dimethoxynaphthalene* (IV).—Compound (III) (1·5 g.) was added in small amounts to nitric acid (*d* 1·5, 15 c.c.) at 0°, with stirring. After standiug for 1 hr., the solution was poured on ice and the precipitate crystallised, first from acetic acid, and then from toluene in light orange rhombic plates, m. p. 255° (gas evolution) (0·4 g.; 23%) (Found: C, 38·9; H, 2·1; N, 14·9. $C_{12}H_8O_{10}N_4$ requires C, 39·1; H, 2·2; N, 15·2%).

2 : 4-*Dinitro*-5-*methoxy*-1-*naphthol* (V) (cf. Hodgson and Smith, *J.*, 1935, 671).—To a stirred suspension of 5-methoxy-1-naphthol (10 g.) in acetic anhydride (40 c.c.) at 0°, an ice-cold solution of diacetyl orthonitric acid (12 c.c.) in acetic anhydride (10 c.c.) was added dropwise during 1 hr. Stirring was continued for 90 mins., after which the mixture was poured on ice, the black precipitate being collected, washed with water, and dried. The product was repeatedly extracted with 2% sodium carbonate solution, and the extracts combined and acidified. The yellow precipitate was crystallised several times from carbon tetrachloride (charcoal), from which it separated in orange needles, m. p. 173° (decomp.) (0·7 g.; 6%) (Found: C, 49·95; H, 3·5; N, 10·6. $C_{11}H_8O_6N_2$ requires C, 50·0; H, 3·0; N, 10·6%). Acetylation of compound (V) with acetic anhydride containing a trace of concentrated sulphuric acid afforded 2 : 4-*dinitro*-1-*acetoxy*-5-*methoxynaphthalene*, fine yellow needles, m. p. 154° (gas evolution) (Found: C, 50·5; H, 3·15; N, 10·0. $C_{13}H_{10}O_7N_2$ requires C, 51·0; H, 3·3; N, 9·15%). Attempts to mononitrate 5-methoxy-1-naphthol were unsuccessful.

2 : 4-*Dinitro*-1 : 5-*dimethoxynaphthalene* (VI).—A suspension of compound (V) (1·4 g.) in ether (50 c.c.) at −10° was methylated with diazomethane, prepared by the action of potassium hydroxide solution (10 c.c., 50%) on nitrosomethylurea (3 g.) in ether (30 c.c.). After 3 hrs., the *product* was collected and crystallised from dilute acetic acid in yellow needles, m. p. 153° (Found: C, 51·5; H, 3·5; N, 10·1 $C_{12}H_{10}O_6N_2$ requires C, 51·8; H, 3·6; N, 10·1%). Nitric acid (*d* 1·5, 5 c.c.) was added to compound (VI) (2 g.) in hot acetic acid (30 c.c.), and the solution refluxed gently for 30 mins. The crystals which separated on cooling (0·4 g.; 17%), after recrystallisation from dilute acetic acid, formed yellow needles, m. p. 180°, identical with compound (III). A solution of compound (VI) (1 g.) in hot acetic acid (10 c.c.) was refluxed gently with nitric acid (*d* 1·5, 5 c.c.) for 30 mins. Crystals were deposited on cooling, and these, when recrystallised from toluene, furnished light orange rhombic plates, m. p. 255° (gas evolution), identical with compound (IV).

8-*Nitro*-1-*acetoxy*-5-*methoxynaphthalene* (VII).—Nitric acid (*d* 1·42, 1·5 c.c.) in acetic acid (3·5 c.c.) was added slowly to a stirred solution of 1-acetoxy-5-methoxynaphthalene (5 g.) in acetic acid (20 c.c.) at room temperature during 1 hr. The mixture was poured on ice, and the product crystallised from dilute acetic acid in golden-yellow needles or plates, m. p. 136° (2·3 g.; 38%) (Found: C, 59·9; H, 4·4; N, 5·5; OMe, 11·0. $C_{13}H_{11}O_5N$ requires C, 59·8; H, 4·2; N, 5·4; OMe, 11·9%).

8-*Nitro*-5-*methoxy*-1-*naphthol* (VIII).—Compound (VII) (2 g.) was hydrolysed by boiling gently with sodium hydroxide solution (20 c.c., 5%) for 5 mins.; the deep red solution was diluted with water, cooled, and acidified, the precipitate which formed being collected and crystallised from dilute alcohol, forming brown needles or plates, m. p. 165° (1·65 g.; 95%) (Found: C, 60·2; H, 4·2; N, 6·1; OMe, 12·5. $C_{11}H_9O_4N$ requires C, 60·3; H, 4·1; N, 6·4; OMe, 14·2%). Compound (VIII) (1 g.) was dissolved in sodium hydroxide solution (220 c.c., 0·125%) and warmed to 30°. Excess of methyl sulphate was added and, after being shaken for 30 mins., the precipitate was collected and crystallised from acetic acid, forming yellow rhombic plates, m.p. 167°, identical with compound (I).

2 : 8-*Dinitro*-5-*methoxy*-1-*naphthol* (IX).—1-Acetoxy-5-methoxynaphthalene (20 g.) was added gradually, with stirring, to nitric acid (*d* 1·42, 100 c.c.) at 0°. The yellow crystals were filtered off, washed with water, and recrystallised from alcohol; yellow needles, m. p. 183° (gas evolution) (8·3 g.; 40%) (Found: C, 49·7; H, 2·9; N, 10·0. $C_{11}H_8O_6N_2$ requires C, 50·0; H, 3·0; N, 10·6%). Concentration of the alcoholic filtrate afforded 6 : 8-dinitro-5-methoxy-1-acetoxynaphthalene (XI) (2·2 g.), m. p. 134°. 2 : 8-*Dinitro*-5-*methoxy*-1-*naphthol* was soluble in alkali, but all attempts to acetylate it were unsuccessful.

2 : 8-*Dinitro*-1 : 5-*dimethoxynaphthalene* (X).—Compound (IX) (1 g.) was suspended in ether (30 c.c.) at −10° and methylated with diazomethane. 2 : 8-*Dinitro*-1 : 5-*dimethoxynaphthalene* crystallised from dilute acetic acid in fine pale yellow needles, m. p. 135° (Found: C, 51·3; H, 3·4; N, 9·7. $C_{12}H_{10}O_6N$ requires C, 51·8; H, 3·9; N, 10·1%).

6 : 8-*Dinitro*-1-*acetoxy*-5-*methoxynaphthalene* (XI).—1-Acetoxy-5-methoxynaphthalene (10 g.) was added gradually with stirring to nitric acid (*d* 1·42, 50 c.c.) at 40°. The mixture was poured on ice, and the precipitate crystallised from alcohol in pale yellow needles or plates, m. p. 134° (1·3 g.; 9%) (Found: C, 51·0; H, 3·25; N, 9·0; OMe, 9·85. $C_{13}H_{10}O_7N_2$ requires C, 51·0; H, 3·3; N, 9·15; OMe, 10·1%).

Both compounds (IX) and (XI) were obtained by nitration of 8-nitro-1-acetoxy-5-methoxynaphthalene, a factor of importance in determining the orientation of the second nitro-group. Diacetyl orthonitric acid (2 c.c.) was added slowly to 8-nitro-1-acetoxy-5-methoxynaphthalene (1 g.) in acetic anhydride (4 c.c.), the temperature rising to 90°. The solution was poured on ice, and the product crystallised from dilute acetic acid in pale yellow needles, m. p. 134° (0·5 g.; 43%), identical with compound (XI). 8-Nitro-1-acetoxy-5-methoxynaphthalene (3·7 g.) was added in small amounts to

nitric acid (*d* 1·42, 18 c.c.) at 5°. The crystals were collected, washed with water, and recrystallised from alcohol in yellow needles, m. p. 183° (gas evolution) (0·5 g.; 13%), identical with compound (IX).

2 : 4-*Dinitro*-1 : 5-*dihydroxynaphthalene* (XII).—Compound (XI) (1·75 g.) was suspended in sodium hydroxide solution (50 c.c., 2%) and refluxed for 10 mins. The dark red solution was cooled and acidified, and the precipitate which formed crystallised from dilute acetic acid in golden-brown needles, m. p. 247° (decomp.) (1 g.; 66%), and contained no methoxyl group (Found: C, 48·4; H, 2·5; N, 10·8. $C_{10}H_6O_6N_2$ requires C, 48·0; H, 2·4; N, 11·2%). Methylation of compound (XII) with diazomethane afforded yellow plates, m. p. 153°, identical with compound (VI), whilst the product of methylation with excess of methyl sulphate in alkaline solution was orange needles, m. p. 173° (decomp.), identical with 2 : 4-dinitro-5-methoxy-1-naphthol (V).

The methoxyl group in compound (XI) (1 g.) was also hydrolysed by vigorously refluxing a suspension in water (800 c.c.) for 5 hrs. The orange solution was filtered and allowed to cool; the small yellow prisms (0·5 g.; 62%) which were deposited recrystallised from alcohol in yellow needles, m. p. 189°, identical with 2 : 4-dinitro-5-acetoxy-1-naphthol (XIV).

6 : 8-*Dinitro*-5-*methoxy*-1-*naphthol* (XIII).—A solution of 6 : 8-dinitro-1-acetoxy-5-methoxynaphthalene (1 g.) in methyl alcohol (40 c.c.) was refluxed with ammonia (*d* 0·880, 0·3 c.c.) for 1 hr. The solution was concentrated to 15 c.c., diluted with water (30 c.c.), and allowed to cool. Crystals (0·6 g.; 66%) were deposited and after several recrystallisations from aqueous methyl alcohol, 6 : 8-*dinitro*-5-*methoxy*-1-*naphthol* formed orange-brown needles, m. p. 202—204° (Found: C, 50·3; H, 3·4; N, 11·6. $C_{11}H_8O_6N_2$ requires C, 50·0; H, 3·0; N, 10·6%).

2 : 4-*Dinitro*-5-*acetoxy*-1-*naphthol* (XIV).—1 : 5-Diacetoxynaphthalene (5 g.) was added in small portions to nitric acid (*d* 1·42, 25 c.c.) at 20°. A crystalline solid separated which, after standing for 30 mins., was collected, washed with water, and crystallised from dilute acetic acid, forming glistening yellow needles, m. p. 189° (3·2 g.; 54%) (Found: C, 48·8; H, 2·8; N, 9·7. $C_{12}H_8O_7N_2$ requires C, 49·3; H, 2·7; N, 9·6%). It could not be acetylated, and 1 : 5-diacetoxynaphthalene could not be mononitrated. Hydrolysis of compound (XIV) with dilute sodium hydroxide solution afforded orange-brown needles, m. p. 247° (decomp.), identical with compound (XII), whilst methylation with diazomethane yielded 6 : 8-dinitro-1-acetoxy-5-methoxynaphthalene (XI), pale yellow needles, m. p. 134°.

2 : 4 : 6-*Trinitro*-5-*acetoxy*-1-*naphthol* (XV).—1 : 5-Diacetoxynaphthalene (30 g.) was added gradually to well-stirred nitric acid (*d* 1·42, 150 c.c.) at 50°. Considerable oxidation occurred and the temperature was lowered to 40° towards the end of the addition, after which the suspension was cooled rapidly to 0°. The product was filtered off and washed with water; it crystallised from acetic acid in yellow needles, m. p. 223° (decomp.) (2·1 g.; 5·1%) (Found: C, 42·6; H, 2·1; N, 12·8. $C_{12}H_7O_9N_3$ requires C, 42·7; H, 2·1; N, 12·5%).

2 : 4 : 6-*Trinitro*-1 : 5-*dihydroxynaphthalene* (XVI).—A suspension of compound (XV) (2·1 g.) in sodium hydroxide solution (20 c.c., 2%) was boiled. The clear deep-red solution was diluted with water and acidified; the precipitate crystallised from dilute acetic acid in yellow needles, m. p. 260° (decomp.) (1·4 g.; 59%) (Found: C, 41·1; H, 1·9; N, 14·2. $C_{10}H_5O_8N_3$ requires C, 40·7; H, 1·7; N, 14·2%).

2 : 4 : 6-*Trinitro*-1 : 5-*dimethoxynaphthalene* (XVII).—Compound (XVI) (1 g.) was suspended in ether (50 c.c.) and methylated with diazomethane. The *product* crystallised from acetic acid in fine yellow needles, m. p. 238° (0·65 g.; 60%) (Found: C, 44·8; H, 3·1; N, 12·7. $C_{12}H_9O_8N_3$ requires C, 44·6; H, 2·8; N, 13·0%).

2 : 4 : 6-*Trinitro*-5-*acetoxy*-1-*methoxynaphthalene* (XVIII).—An ethereal suspension of compound (XV) (1·2 g.) was treated with diazomethane and the product crystallised from acetic acid in pale yellow needles, m. p. 184° (Found: C, 44·7; H, 2·8; N, 12·2; OMe, 9·2. $C_{13}H_9O_9N_3$ requires C, 44·4; H, 2·6; N, 12·0; OMe, 8·8%). It behaved in a similar manner to 6 : 8-dinitro-1-acetoxy-5-methoxynaphthalene, being hydrolysed by dilute sodium hydroxide solution to 2 : 4 : 6-trinitro-1 : 5-dihydroxynaphthalene (XVI), whilst boiling water demethylated it with formation of 2 : 4 : 6-trinitro-5-acetoxy-1-naphthol (XV).

2 : 4 : 6 : 8-*Tetranitro*-1 : 5-*dihydroxynaphthalene* (XIX).—Compound (XIV) (6 g.) was added gradually to nitric acid (*d* 1·5, 12 c.c.) at 0°. After standing for 30 mins., the suspension was filtered off, washed with water, and dried. Fractional crystallisation from acetone afforded a little unchanged compound (XIV) (0·45 g.), together with 2 : 4 : 6 : 8-*tetranitro*-1 : 5-*dihydroxynaphthalene*, small yellow needles, which decomposed violently between 250° and 265° according to the rate of heating (1·1 g.; 16%) (Found: C, 35·15; H, 1·4; N, 15·5. $C_{10}H_4O_{10}N_4$ requires C, 35·3; H, 1·2; N, 16·5%).

Direct nitration of 1 : 5-dihydroxynaphthalene also afforded the tetranitro-derivative. An ice-cold solution of diacetyl orthonitric acid (7 c.c.) in acetic anhydride (10 c.c.) was run slowly into a stirred suspension of 1 : 5-dihydroxynaphthalene (5 g.) in acetic anhydride (30 c.c.) at 0° during 1½ hrs. The dark brown mixture was poured on ice, and the black precipitate collected, washed, and dried. After extraction with acetic acid and concentration of the extract (charcoal) to small bulk, brown needles were deposited on cooling, and these, when recrystallised from acetone, formed yellow needles decomposing violently at 250—265° (0·6 g.; 6%). The compound was sparingly soluble in most organic solvents, and coloured red by alkalis without dissolution. Methylation with diazomethane gave 2 : 4 : 6 : 8-tetranitro-1 : 5-dimethoxynaphthalene (IV).

2 : 6-*Dinitro*-1 : 5-*dihydroxynaphthalene* (XX) (cf. Mencke, *Rec. Trav. chim.*, 1925, **44**, 269).—A suspension of 1 : 5-dihydroxynaphthalene (20 g.) in acetic acid (100 c.c.) was added slowly to a well-stirred suspension of copper nitrate (20 g.) in acetic anhydride (50 c.c.) at 10°, and the temperature was then allowed to rise slowly to 25°. After gentle effervescence had occurred, the mixture was stirred for 15 mins. below 40° and poured into water. The precipitate was collected, washed, dried, and repeatedly extracted with dilute sodium carbonate solution. The violet-red extracts were combined and acidified, the precipitate which formed crystallising from acetic acid (charcoal) in glistening orange leaflets, m. p. 246° (decomp.) (0·5 g.; 1·6%) (Found: C, 49·1; H, 2·6; N, 11·4. $C_{10}H_6O_6N_2$ requires C, 48·0; H, 2·4; N, 11·2%).

2 : 6-*Dinitro*-1 : 5-*dimethoxynaphthalene* (XXI).—Compound (XX) was methylated with diazomethane and crystallised from acetic acid in fine straw-coloured needles, m. p. 222° (Found: C, 51·8; H, 3·6; N, 8·9. $C_{12}H_{10}O_6N_2$ requires C, 51·8; H, 3·9; N, 10·1%).

4-*Amino*-1 : 5-*dimethoxynaphthalene* (XXII).—Compound (I) (10 g.), granulated tin (15 g.), and hydrochloric acid (100 c.c.) were refluxed for 3 hrs. The hydrochloride, which separated on cooling, recrystallised from dilute hydrochloric acid in minute grey plates, decomposing without melting at 264° (approx.) (10 g.; 97%). The hydrochloride was dissolved in dilute hydrochloric acid (600 c.c.) and basified with sodium hydroxide solution. The *base* crystallised from alcohol in glistening leaflets, m. p. 160° (4·1 g.; 47%) (Found: C, 70·8; H, 6·8; N, 7·0. $C_{12}H_{13}O_2N$ requires C, 70·9; H, 6·4; N, 6·9%), readily oxidisable and becoming violet in air. When this was warmed with acetic anhydride the *monoacetyl* derivative was obtained, crystallising from alcohol in colourless needles or plates, m. p. 186° (Found: C, 68·4; H, 6·1; N, 5·6. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%). The base was diazotised in dilute hydrochloric acid at −10° and coupled with β-naphthol in alkaline solution; 1 : 5-*dimethoxynaphthaleneazo-β-naphthol* crystallised from toluene in bronze-green needles, m. p. 214° (Found: C, 73·6; H, 5·3; N, 8·2. $C_{22}H_{18}O_3N_2$ requires C, 73·7; H, 5·1; N, 8·0%).

4-*Bromo*-1 : 5-*dimethoxynaphthalene*.—The hydrochloride (6 g.) of compound (XXII) was boiled with water (100 c.c.) and hydrochloric acid (4·5 c.c.), the solution being cooled rapidly to 0°. Sodium nitrite solution was added slowly beneath the surface, with stirring. After 15 mins. the diazo-solution was filtered, added in portions to cuprous bromide solution at 0°, with shaking between additions, and the mixture warmed on the water-bath for 30 mins. until evolution of nitrogen ceased. The product was filtered off, washed, dried, and extracted with alcohol (charcoal), the extract being concentrated to small bulk and diluted with water. 4-Bromo-1 : 5-dimethoxynaphthalene recrystallised from dilute alcohol in colourless leaflets, m. p. 106·5° (0·2 g.; 3%) (Found: Br, 29·7. Calc. for $C_{12}H_{11}O_2Br$: Br, 29·9%) (cf. Fischer and Bauer, *loc. cit.*, who recorded m. p. 115°), identical with the product of monobromination of 1 : 5-dimethoxynaphthalene.

8-*Nitro*-4-*amino*-1 : 5-*dimethoxynaphthalene* (XXIII).—Sodium sulphide (24 g.) in water (150 c.c.) was added to a suspension of compound (II) (8 g.) in alcohol (500 c.c.), refluxed vigorously for 1 hr., and the dark red-brown solution then filtered and concentrated to 400 c.c. The nitro-amine, which was deposited on cooling, recrystallised from alcohol in glistening orange leaflets, m. p. 200° (6·07 g.; 94%) (Found: C, 56·7; H, 4·8; N, 10·8. $C_{12}H_{12}O_4N_2$ requires C, 58·0; H, 4·8; N, 11·3%). The *acetyl* derivative, obtained when the base was warmed with acetic anhydride and poured into water, crystallised from alcohol in flat yellow needles, m. p. 209° (Found: C, 56·4; H, 4·6; N, 9·7. $C_{14}H_{14}O_5N_2$ requires C, 57·9; H, 4·8; N, 9·7%). The base was diazotised in hydrochloric acid at 0° and coupled with β-naphthol in alkaline solution. 8-*Nitro*-1 : 5-*dimethoxynaphthaleneazo-β-naphthol* crystallised from nitrobenzene in minute reddish-brown prisms with a green reflex, m. p. 280° (Found: C, 64·6; H, 4·2; N, 10·1. $C_{22}H_{17}O_5N_3$ requires C, 65·5; H, 4·2; N, 10·3%).

4 : 8-*Diamino*-1 : 5-*dimethoxynaphthalene* (XXIV).—Compound (II) (25 g.), granulated tin (50 g.), and hydrochloric acid (300 c.c.) were refluxed for 3 hrs. The solid which was deposited on cooling was recrystallised from dilute hydrochloric acid, forming fine colourless needles, charring at 280° (approx.) without melting (20 g.; 70%) (Found: C, 49·4; H, 5·7; N, 9·8; Cl, 23·4. $C_{12}H_{16}O_2N_2Cl_2$ requires C, 49·5; H, 5·5; N, 9·6; Cl, 24·4%). The *hydrochloride* was dissolved in dilute hydrochloric acid (1000 c.c.) and basified with sodium hydroxide solution. The *base* (13 g.; 66%) crystallised with difficulty from alcohol in minute violet crystals with a metallic lustre, m. p. 180° (Found: C, 65·8; H, 6·5; N, 12·8. $C_{12}H_{14}O_2N_2$ requires C, 66·0; H, 6·4; N, 12·8%), sparingly soluble in most organic solvents with a faint bluish-violet fluorescence, and rapidly oxidised in air. The *diacetyl* derivative, obtained by refluxing the base with acetic anhydride and pouring on ice, crystallised from acetic anhydride (charcoal) in colourless rhombic plates, m. p. 304° (Found: C, 63·6; H, 5·9; N, 10·3. $C_{16}H_{18}O_4N_2$ requires C, 63·6; H, 6·0; N, 9·3%).

8-*Amino*-1-*acetoxy*-5-*methoxynaphthalene* (XXV).—Compound (VII) (10 g.) was refluxed with sodium hyposulphite (dithionite) (30 g.), alcohol (200 c.c.), and water (70 c.c.) for 2 hrs., and the solution filtered and diluted with water (500 c.c.). The solid which was deposited on keeping crystallised from alcohol in pale brown needles, m. p. 154° (2·2 g.; 24%) (Found: C, 67·4; H, 5·8; N, 6·4. $C_{13}H_{15}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

5-*Methoxy*-1 : 4-*naphthaquinone* (XXVI).—4-Amino-1 : 5-dimethoxynaphthalene hydrochloride (10 g.) was dissolved in boiling water (1000 c.c.) containing concentrated sulphuric acid (30 c.c.), and oxidised with potassium dichromate solution (800 c.c., 1·25%), the mixture being warmed to 60—70° until the quinone began to separate. 5-*Methoxy*-1 : 4-*naphthaquinone* was collected; it crystallised from alcohol in orange-brown prismatic needles, m. p. 189° (3·8 g.; 48%) (Found: C, 70·0; H, 4·35; OMe, 17·2. $C_{11}H_8O_3$ requires C, 70·2; H, 4·3; OMe, 16·5%). The *oxime*, obtained by refluxing the quinone with hydroxylamine hydrochloride in alcoholic solution, crystallised in fine yellow needles, m. p. 233° (decomp.) (Found: C, 64·3; H, 4·5; N, 6·6. $C_{11}H_9O_3N$ requires C, 65·0; H, 4·4; N, 6·9%). 5-*Methoxy*-1 : 4-*naphthaquinone* 2 : 4-*dinitrophenylhydrazone* crystallised from nitrobenzene in small dark red needles, m. p. 286° (decomp.) (Found: C, 55·6; H, 3·2; N, 14·85. $C_{17}H_{12}O_6N_4$ requires C, 55·4; H, 3·3; N, 15·2%). The quinone was reduced by phenylhydrazine in boiling alcoholic solution to 5-*methoxy*-1 : 4-*dihydroxynaphthalene*, which crystallised from benzene in colourless needles, m. p. 190° (Found: C, 69·6; H, 5·3. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

Oxidation of 8-*Amino*-1-*acetoxy*-5-*methoxynaphthalene*.—The base (3·25 g.) was suspended in acetic acid (40 c.c.), and a solution of chromium trioxide (6·5 g.) in water (13 c.c.) added rapidly with stirring. A vigorous reaction occurred, the temperature rising to 80°. The crystals deposited on cooling recrystallised from acetic acid in minute red needles, m. p. >350°. The product was not a quinone and was not identified (Found: C, 61·8; H, 4·6; N, 6·5%).

Oxidation of 4-*Nitro*-1 : 5-*dimethoxynaphthalene to* 6-*Nitro*-3-*methoxyphthalic Anhydride* (XXVII).—A suspension of the nitro-compound (10 g.) in dilute nitric acid (*d* 1·14, 750 c.c.) was refluxed vigorously for 5 hrs. The resultant solid, which was filtered off, was 4 : 8-dinitro-1 : 5-dimethoxynaphthalene and crystallised from acetic acid in yellow needles, m. p. 275°. The filtrate was evaporated to dryness and the residue separated from ether–ligroin as a sticky yellow solid. Recrystallisation from nitrobenzene afforded 6-*nitro*-3-*methoxyphthalic anhydride* in cream-coloured plates, m. p. 164—165° (Found: C, 48·5; H, 2·3; N, 6·55. $C_9H_5O_6N$ requires C, 48·4; H, 2·2; N, 6·3%). The anhydride gave the

fluorescein reaction when fused with resorcinol, but did not react with sodium bicarbonate solution, and the acid (XXVIII) was obtained by acidifying an alkaline solution of the anhydride.

Oxidation of 4 : 8-*Dinitro*-1 : 5-*dimethoxynaphthalene to* 6-*Nitro*-3-*methoxyphthalic Acid* (XXVIII).—4 : 8-Dinitro-1 : 5-dimethoxynaphthalene (10 g.) was refluxed with nitric acid (*d* 1·14, 750 c.c.) for 2 hrs., the solution filtered, and the filtrate evaporated to dryness on the water-bath. The residue was extracted with ether, and the extract diluted with ligroin. After several crystallisations from ether–ligroin 6-*nitro*-3-*methoxyphthalic acid* was obtained in small colourless prisms, m. p. 179—180° (gas evolution), which became opaque and coloured on drying (1 g.; 12%) (Found : C, 44·8; H, 3·0; N, 5·7. $C_9H_7O_7N$ requires C, 44·7; H, 2·9; N, 5·8%). The acid dissolved in water with a yellow colour, liberated carbon dioxide from sodium bicarbonate solution, and gave a positive fluorescein reaction when fused with resorcinol.

Oxidation of 2 : 4-*Dinitro*-5-*acetoxy*-1-*naphthol to* 4 : 6-*Dinitro*-3-*hydroxyphthalic Acid* (*Ammonium Salt*) (XXIX).—A suspension of the naphthol (10 g.) in dilute nitric acid (*d* 1·15, 140 c.c.) was refluxed for 1½ hrs., filtered, diluted with water (50 c.c.), and cooled. The solution was extracted with ether, and the ether removed in a stream of air. The residue was very soluble in water, alcohol, and ether, insoluble in ligroin, and gave the fluorescein reaction when fused with resorcinol. 4 : 6-Dinitro-3-hydroxyphthalic acid was isolated as the ammonium salt, which crystallised under reduced pressure from a little water containing a drop of ammonia in brownish-yellow plates, or, when cooled rapidly, in yellow needles (1·2 g.; 17%) (Found : C, 31·2; H, 3·2; N, 18·5. Calc for $C_8H_{10}O_9N_4$: C, 31·4; H, 3·3; N, 18·3%) (cf. Bernthsen and Semper, *Ber.*, 1885, **18**, 204).

Action of Ammonia and Methylamine on Nitro-1 : 5-*dimethoxynaphthalenes*.—4-Nitro-1 : 5-dimethoxynaphthalene and 4 : 8-dinitro-1 : 5-dimethoxynaphthalene did not react with ammonia in a sealed tube at 200°.

2 : 4-Dinitro-1 : 5-dimethoxynaphthalene (0·5 g.) in alcohol (30 c.c.) was refluxed for 2 hrs. with ammonia (*d* 0·880, 2 c.c.). 2 : 4-*Dinitro*-5-*methoxy*-1-*naphthylamine* crystallised from alcohol in fine orange-yellow needles, m. p. 225° (Found : C, 50·5; H, 3·7; N, 15·5. $C_{11}H_9O_5N_3$ requires C, 50·2; H, 3·4; N, 16·0%). The *acetyl* derivative, obtained by warming the base with acetic anhydride containing a drop of concentrated sulphuric acid, crystallised from dilute acetic acid in yellow, feathery needles, m. p. 262° (Found : C, 51·3; H, 3·7; N, 14·3. $C_{13}H_{11}O_6N_3$ requires C, 51·2; H, 3·6; N, 13·8%). Similarly, 2 : 4 : 8-trinitro-1 : 5-dimethoxynaphthalene, when refluxed in alcoholic solution with excess of methylamine, yielded 2 : 4 : 8-*trinitro*-1-*methylamino*-5-*methoxynaphthalene*, crystallising from dilute acetic acid in orange needles, m. p. 204° (Found : C, 44·7; H, 3·2; N, 17·4. $C_{12}H_{10}O_7N_4$ requires C, 44·7; H, 3·1; N, 17·4%).

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.

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71. *Experiments on the Synthesis of Purine Nucleosides. Part XVI. 9-β-d-Mannopyranosidoadenine. A Proof of the Location of the Sugar Residue in Adenosine.*

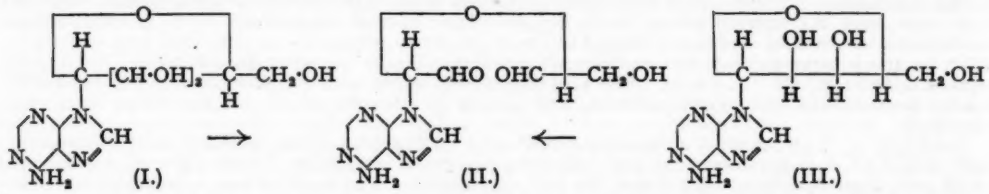
By B. LYTHGOE, H. SMITH, and A. R. TODD.

Following the general procedure established in earlier papers of this series, 9-d-*mannopyranosido*-2-*methylthioadenine* has been synthesised and converted by a desulphurisation procedure into 9-d-*mannopyranosidoadenine*. Since the latter compound yields on periodate oxidation a dialdehyde (isolated as its *picrate*) identical with that obtained on similar oxidation of adenosine, it follows that the ribofuranose residue in the natural compound is located at N_9 in the purine skeleton. It also follows that the synthetic mannoside has a β-configuration at the glycosidic carbon atom.

IN applying the route for the synthesis of 9-glycosidopurine derivatives described in previous papers (Part IX, *J.*, 1944, 652; Part X, *J.*, 1944, 657; Part XI, *J.*, 1945, 556) attention has so far been directed to pentoside representatives of the series on account of their closer relationship to the naturally occurring nucleosides. The extension of our method to the synthesis of a hexoside analogue forms the subject of the present communication. This work was undertaken not merely with the object of enlarging the range of synthetic adenine glycosides available, but also because it seemed to offer an opportunity of testing by direct chemical methods the N_9 allocation of the sugar residue in adenosine. This allocation, due to Gulland and Holiday (*J.*, 1936, 765), rests at present upon the similarity of the ultra-violet absorption spectra of adenosine and related purine derivatives bearing a substituent on N_9.

Study of the products obtained by oxidation of adenosine and related glycosides with sodium metaperiodate has shown that the glycosidic linkage in adenosine is of the β-type (Part XII, *J.*, 1946, 833). The 9-*d*-glycopyranosidoadenine derivatives so far prepared by our synthetic route have also the β-configuration (Part XII, *loc. cit.*; Part XV, *J.*, 1946, 861) and, since the nature of the method employed permits the formation only of N_9- and not of N_7-glycosidopurines, it seemed likely that by use of a *d*-hexose an authentic 9-β-*d*-hexopyranosidoadenine (I) would

be obtained. Such a compound should give rise on oxidation with sodium metaperiodate to the same dialdehyde (II) as results from the fission of adenosine (III) with the same reagent, provided that (III) is, in fact, a 9-glycoside.



In order to test this we commenced (with Mr. A. Holland) the synthesis of adenine-9-*d*-glucopyranoside, in the hope that the product would prove to be identical with the adenine glucoside first synthesised by Fischer and Helferich (*Ber.*, 1914, **47**, 210); we have already shown (Part XII, *loc. cit.*) that the latter glucoside gives rise on periodate oxidation to the same dialdehyde as does adenosine, but the evidence that the glucose residue is situated at N_9 is, as in the case of adenosine, based on study of the ultra-violet absorption spectrum (Gulland and Story, *J.*, 1938, 259). Work on the synthesis of the authentic adenine-9-*d*-glucopyranoside is not yet complete, as the yields obtained in some of the stages are not altogether satisfactory, so that an account of this work is at present deferred. As a more suitable alternative, the synthesis of 9-*d*-mannopyranosidoadenine was undertaken.

Starting material for the synthesis of this mannoside was readily accessible in the crystalline 6-amino-4-*d*-mannosidamino-2-methylthiopyrimidine, prepared as described in Part III (*J.*, 1943, 571). Introduction of a nitrogen into the pyrimidine nucleus at C_5 was achieved by use of nitrous acid (cf. Part XI, *loc. cit.*) giving *5-nitroso-6-amino*-4-d-*mannosidamino-2-methylthiopyrimidine*, which was converted by standard methods into *6-amino-5-thioformamido*-4-d-*mannosidamino-2-methylthiopyrimidine*. When the latter was subjected to cyclisation with sodium methoxide in ethanol (Part XIII, *J.*, 1946, 852), 9-d-*mannopyranosido-2-methylthioadenine* was isolated; no 6-*d*-mannosidaminopurine derivative could be detected in the cyclisation product. The constitution of the product was confirmed by its insolubility in dilute alkali and by deamination to 9-d-*mannopyranosido-2-methylthiohypoxanthine*, and its ring-structure was determined by titration with sodium metaperiodate When *9-tetra-acetyl*-d-*mannopyranosido-2-methylthioadenine*, prepared by acetylation of the corresponding mannoside, was refluxed in alcohol with Raney nickel prepared according to Mozingo (*J. Amer. Chem. Soc.*, 1943, **65**, 1013) it underwent desulphurisation (cf. Part XI, *loc. cit.*), and deacetylation of the crude reaction product with methanolic ammonia gave 9-d-*mannopyranosidoadenine*.

This mannoside reacted with sodium metaperiodate with uptake of 2 mols. of oxidant and liberation of 1 mol. of formic acid; the fission product (isolated as the *picrate*) proved identical with samples obtained from similar oxidation of adenosine and of Fischer and Helferich's adenine glucoside. From this identity it follows that the ribofuranose residue in adenosine is located at N_9 in the purine nucleus and that the synthetic mannoside is correctly described as 9-β-*d*-mannopyranosidoadenine.

Experimental.

5-Nitroso-6-amino-4-d-mannosidamino-2-methylthiopyrimidine.—6-Amino-4-*d*-mannosidamino-2-methylthiopyrimidine (4 g.; Part III, *loc. cit.*) dissolved in water (200 c.c.) was treated at 0° with sodium nitrite (2·5 g.) and glacial acetic acid (7 c.c.); after 1 hour at 0° the solution was kept at room temperature for a further hour, and the blue precipitate collected and washed with ice-water. Recrystallisation from water gave fine purple needles of the *nitroso*-compound, m. p. 230—231° (decomp.) (2·8 g.) (Found in material dried at 110°: C, 36·4; H, 5·3; N, 18·7. $C_{11}H_{17}O_6N_5S$ requires C, 36·2; H, 5·2; N, 19·2%).

6-Amino-5-thioformamido-4-d-mannosidamino-2-methylthiopyrimidine.—The above nitroso-compound (8 g.) was suspended in ice-water (350 c.c.) and after addition of a solution of ammonium sulphide [30 c.c. of ammonia (*d* 0·88) and 350 c.c. of water saturated with hydrogen sulphide at 0°] a current of hydrogen sulphide was passed through the cooled suspension for 6 hours; unchanged nitroso-compound (*ca.* 1 g.) was then removed by filtration. The filtrate was evaporated to dryness under reduced pressure at 25°, the residue extracted with hot water (700 c.c.), and the filtered extract cooled in an atmosphere of nitrogen and treated with sodium dithioformate solution (54 g. of hexahydrate in 180 c.c. of water). After 48 hours the *thioformyl* compound was collected and a further crop obtained by concentration of the mother liquors to 500 c.c. below 25°. Recrystallised from water (charcoal) it formed clusters of colourless needles, m. p. 217—219° (decomp.) (4 g.) (Found in material dried at 110°/0·1 mm. over phosphoric oxide: C, 36·4; H, 5·6; N, 17·5. $C_{12}H_{19}O_5N_5S_2,H_2O$ requires C, 36·6; H, 5·3; N, 17·7%). In one experiment in which sodium dithioformate solution was added to a warm (50°) solution of the crude product of ammonium sulphide reduction of the nitroso-compound, the above thioformyl derivative was accompanied by a small quantity of material, m. p. 231—232° (decomp., without evolution of

hydrogen sulphide). From its behaviour this was presumably 6-*amino*-5-*formamido*-4-d-*mannosidamino*-2-*methylthiopyrimidine* formed by hydrolysis of the thioformyl compound (cf. Part XI, *loc. cit.*) (Found in material dried at 140°/0·1 mm. over phosphoric oxide: C, 38·6; H, 5·0; N, 18·7. $C_{12}H_{19}O_6N_5S,H_2O$ requires C, 38·2; H, 5·5; N, 18·5%).

9-d-*Mannopyranosido*-2-*methylthioadenine*.—The thioformyl compound (180 mg.) and sodium methoxide (30 mg.) were heated under reflux in dry ethanol (10 c.c.) with exclusion of moisture for 4 hours, and the mixture set aside at room temperature for 1 hour. The precipitate, collected and recrystallised from water (charcoal), gave 9-d-*mannopyranosido*-2-*methylthioadenine* as long fine colourless needles, m. p. 287—288° (decomp.) (86 mg.), whose solubility in water was not increased by adding sodium hydroxide; $[\alpha]_D^{18°}$ + 58° (*c*, 0·464 in 0·1N-hydrochloric acid) (Found in material dried at 110°/0·1 mm. over phosphoric oxide: C, 39·9; H, 5·4; N, 19·2. $C_{12}H_{17}O_5N_5S,H_2O$ requires C, 39·9; H, 5·3; N, 19·4%. Found in material dried at 140°/0·1 mm. over phosphoric oxide: C, 42·0; H, 4·7. $C_{12}H_{17}O_5N_5S$ requires C, 42·0; H, 4·9%). From the mother liquors further small quantities of the same material were obtained, but complete purification of this was difficult owing to its contamination with 6-amino-5-formamido-4-*d*-mannosidamino-2-methylthiopyrimidine. No evidence for the presence of 6-*d*-mannosidamino-2-methylthiopurine in the cyclisation product could be obtained.

Hydrolysis. 9-*d*-Mannopyranosido-2-methylthioadenine (60 mg.) dissolved in sulphuric acid (4 c.c. of N) was heated under reflux for 4 hours, the solution cooled and neutralised with sodium hydroxide, and the precipitated 2-methylthioadenine filtered off and recrystallised from water (20 mg.); m. p. 296—297°, undepressed in admixture with an authentic specimen. The filtrate, treated with phenylhydrazine hydrochloride (30 mg.) and sodium acetate (60 mg.) and heated to 50°, gave, on cooling, *d*-mannose phenylhydrazone, m. p. 189—190°, undepressed in admixture with authentic material.

Periodate titration. Amount of anhydrous mannoside used, 32·5 mg. Periodate consumed after 60 hours, 2·97 mols. per mol. of mannoside, of which 1 mol. is to be ascribed to oxidation of the methylthio-group (Part XI, *loc. cit.*). Formic acid liberated, 0·98 mol. per mol. of mannoside. The compound is therefore a pyranoside.

9-d-*Mannopyranosido*-2-*methylthiohypoxanthine*.—A solution of the adenine mannoside (114 mg.) in water (10 c.c.) and hydrochloric acid (5 c.c. of N) was treated at 65° with sodium nitrite (229 mg.). After 20 minutes at this temperature, gas evolution had ceased; a further quantity (115 mg.) of sodium nitrite was then added and the heating continued for a further 10 minutes. The solution was finally cooled, neutralised with sodium hydroxide, concentrated under reduced pressure to 15 c.c., and set aside for 60 hours. The product, collected and recrystallised from water, gave 9-d-*mannopyranosido*-2-*methylthiohypoxanthine* (25 mg.) as colourless needles, m. p. 219—220° (decomp.) after sintering at 176° (Found in material dried at 110°/0·1 mm. over phosphoric oxide: C, 40·1; H, 5·0; N, 16·0. $C_{12}H_{16}O_6N_4S,H_2O$ requires C, 39·8; H, 5·0; N, 15·5%).

9-*Tetra-acetyl*-d-*mannopyranosido*-2-*methylthioadenine*.—The adenine mannoside (230 mg.), pyridine (15 c.c.), and acetic anhydride (1·5 c.c.) were shaken together for 3½ hours; dissolution was then complete. Next day the solution was concentrated to 5 c.c., treated with alcohol (10 c.c.), and after 20 minutes evaporated to dryness under reduced pressure. The residue was again evaporated with alcohol and then crystallised from the same solvent, giving the *tetra-acetyl* derivative as plates (275 mg.), m. p. 182—183° (Found in material dried in a vacuum at 110°: C, 46·9; H, 4·9; N, 13·8. $C_{20}H_{24}O_9N_5S$ requires C, 46·9; H, 4·9; N, 13·7%).

9-d-*Mannopyranosidoadenine*.—The tetra-acetyl derivative (200 mg.) in alcohol (30 c.c.) was refluxed with Raney nickel containing adsorbed hydrogen (4 g.; Mozingo, *loc. cit.*) and the solution filtered. The nickel was thoroughly extracted with boiling alcohol (Soxhlet), extracts and filtrate were combined, suspended nickel was removed by centrifugation, and the clear solution was evaporated to dryness in a vacuum. The gummy residue was set aside at 0° for 3 days with methanolic ammonia (30 c.c. saturated at 0°), then filtered and evaporated to dryness under reduced pressure. Recrystallisation from water gave 9-d-*mannopyranosidoadenine* (43 mg.) as long fine needles, m. p. 174·5—176·5° (decomp. at 229°); $[\alpha]_D^{16°}$ + 35° (calc. as anhydrous material) (*c*, 0·325 in water) (Found in material dried at 140°/0·1 mm. over phosphoric oxide: C, 43·1; H, 5·4; N, 23·2. $C_{11}H_{15}O_5N_5,\frac{1}{2}H_2O$ requires C, 43·1; H, 5·2; N, 22·9%). The *picrate*, obtained by mixing alcoholic solutions of the two compounds, formed platelets, m. p. 219° (Found in material dried over phosphoric oxide at 140°/0·1 mm.: C, 39·0; H, 3·9; N, 21·1. $C_{11}H_{15}O_5N_5,C_6H_3O_7N_3$ requires C, 38·8; H, 3·6; N, 21·3%).

Fissions with Sodium Metaperiodate.—9-d-*Mannopyranosidoadenine*. *Titrimetric and polarimetric investigation*. Amount of glycoside used, 17·6 mg. of hemihydrate (in a total volume of 3 c.c. containing 0·645 c.c. of 0·249M-sodium metaperiodate). Amount of periodate consumed, 1·95 mols. per mol. of glycoside. Amount of formic acid liberated, 0·95 mol. per mol. of glycoside. Rotation of solution (final value, after 36 hours at 14°, calculated for anhydrous fission product), $[\alpha]_D^{14°}$ — 20·8°. This value is in good agreement with the values obtained under closely parallel conditions (Part XII, *loc. cit.*) with adenosine (— 20·9°) and with Fischer and Helferich's adenine glucoside (— 21·3°).

9-d-*Mannopyranosidoadenine picrate*. The anhydrous picrate (124 mg.) was kept for 96 hours at room temperature with 0·238M-sodium metaperiodate (7 c.c.); titration then showed fission to be complete. Amount of periodate consumed, 2·0 mols. per mol. of glycoside. The powdery dialdehyde picrate was collected, washed with water, and dried over phosphoric oxide at 110°/0·1 mm. (73 mg.) (Found: C, 37·6; H, 2·9; N, 22·0. Calc. for $C_{10}H_{11}O_4N_5,C_6H_3O_7N_3,H_2O$: C, 37·6; H, 3·1; N, 21·9%); $[\alpha]_D^{17°}$ — 20° (*c*, 1·437 in 0·1N-sodium bicarbonate), in agreement with the value of — 21·2° found for the dialdehyde picrate from adenosine and — 20·7° for that from adenine glucoside (Part XII, *loc. cit.*). The product showed the same behaviour on heating as did the picrates mentioned above.

We thank the Department of Scientific and Industrial Research for a Maintenance Grant held by one of us (H. S.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 20th*, 1946.]

72. *The Crystal Structure of Pyrene. A Quantitative X-Ray Investigation.*

By J. Monteath Robertson and J. G. White.

The crystal and molecular structure of pyrene has been determined by quantitative *X*-ray analysis. The molecular arrangement is more complicated than in anthracene or coronene because the unit cell contains four molecules and these do not coincide with any crystallographic element of symmetry. Nevertheless, the final results show that the molecule does contain an inherent centre of symmetry, in conformity with the chemical evidence, although this centre is not used in building the crystal structure. In the final analysis, direct measurements of the positions of 9 out of the 16 carbon atoms can be made from the Fourier maps, and the positions of the others can be estimated with a good deal of certainty. The bond-length measurements are not so accurate as in the coronene analysis, owing to less favourable resolution, and the possible errors may be as much as $\pm$ 0·03 or $\pm$ 0·04 A. However, the most probable atomic positions indicate bond-length variations in different parts of the molecule, the distances varying from 1·39 to 1·45 A. Details are given in Fig. 4. A rough qualitative explanation of these variations can be given in terms of the 6 stable valency bond structures applicable to pyrene, and the usual Pauling–Brockway bond character–distance curve.

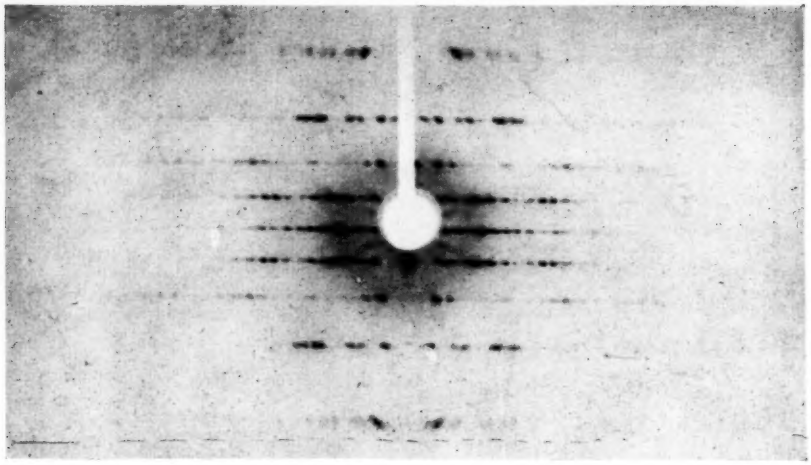
We recently made definite measurements of variable carbon–carbon bond lengths in the aromatic hydrocarbon coronene (*J.*, 1945, 607) and these variations can be given at least a rough qualitative explanation in terms of the 20 non-excited valency bond structures applicable to coronene. A more rigorous treatment of the problem by the molecular orbital method has been attempted by Coulson (*Nature*, 1944, **154**, 797) and these results also receive some support from the *X*-ray measurements.

The extension of such measurements to other condensed-ring aromatic hydrocarbons is obviously a matter of importance, but the work is beset with considerable difficulties. The expected bond-length variations (0·01—0·05 A.) are of just about the same order as the errors which frequently arise even in careful and reasonably quantitative *X*-ray work. Further, the coronene crystal structure is of a type which yields a particularly clear two-dimensional resolution of all the atoms in the molecule by Fourier series methods, and so it represents a specially favourable case for accurate bond-length determination. In the general case we must expect less sharply defined results, unless full three-dimensional Fourier methods are employed. For complicated structures the use of such methods is a formidable task, and in any case they must be preceded by some preliminary analysis, carried out with as much accuracy as possible.

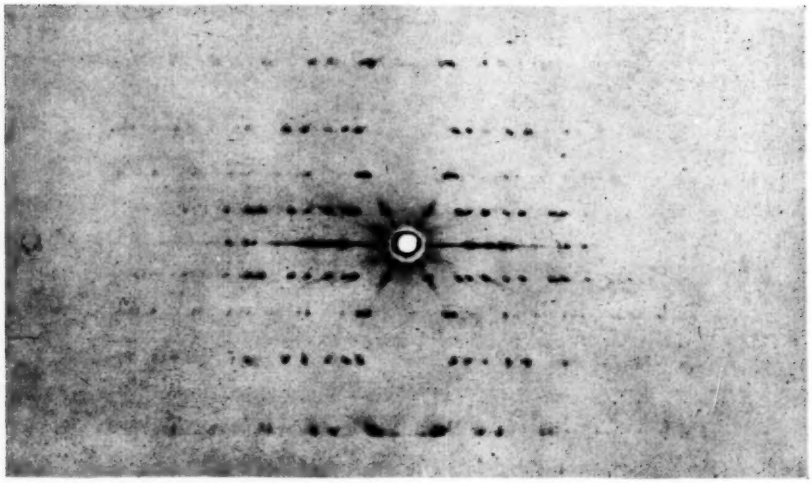
In the present paper we describe such a preliminary analysis, by two-dimensional Fourier series methods, of the crystal structure of pyrene. The arrangement in the crystal is much more complicated than that of coronene, because the unit cell contains four molecules and these do not contain any symmetry element. On general chemical grounds one expects the pyrene molecule to contain a centre of symmetry, and this is very likely true; but the molecular centre is found to occupy a general position which does not coincide with any of the crystallographic centres of symmetry. In other words, it is not used in building the crystal structure. With regard to the orientation of the molecule in the crystal, we find that the inclination of the molecular plane to the symmetry axis is not very different from what it is in coronene or in the phthalocyanines. Nevertheless, in our principal Fourier projection (Fig. 2) only 9 out of the 16 carbon atoms are separately resolved, owing to the overlapping effects of adjoining molecules. This greatly limits the amount of accurate information which can be derived in a direct manner from the present analysis, but in spite of this some significant bond-length variations can be detected, and a reasonable model for the whole molecule can be constructed.

Description of the Structure.—Crystal data. Pyrene, $C_{16}H_{10}$; *M*, 202·2; m. p. 150°; *d*, calc. 1·288, found (Dhar and Guha) 1·27; monoclinic prismatic, $a = 13{\cdot}60 \pm 0{\cdot}05$, $b = 9{\cdot}24 \pm 0{\cdot}03$, $c = 8{\cdot}37 \pm 0{\cdot}10$ A., $\beta = 100{\cdot}2° \pm 0{\cdot}2°$. Absent spectra, $(h0l)$ when h is odd; $(0k0)$ when k is odd. Space-group, $C_{2h}^5(P2_1/a)$. Four molecules per unit cell. No molecular symmetry. Volume of the unit cell, 1035 A.^{3}. Absorption coefficient for *X*-rays, $\lambda = 1{\cdot}54$, $\mu = 6{\cdot}76$ per cm.; $\lambda = 0{\cdot}71$, $\mu = 0{\cdot}86$ per cm. Total number of electrons per unit cell = F(000) = 424.

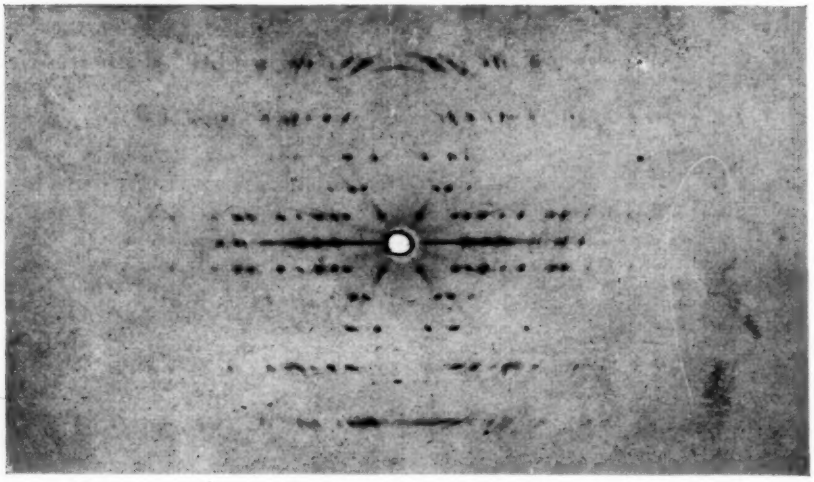
Further goniometric and optical crystal data are given by Groth ("Chemische Krystallographie", 1919, **5**, 437), and the crystal structure has been investigated by Dhar and Guha (*Z. Krist.*, 1935, **91**, 123). The lattice contents given by Dhar and Guha, particularly a and β, differ appreciably from ours. Their *X*-ray work was carried out by means of rotation and oscillation photographs, and leads to a determination of the space-group. They suggest



Pyrene.



Naphthalene.



Anthracene.

[*To face p.* 359.

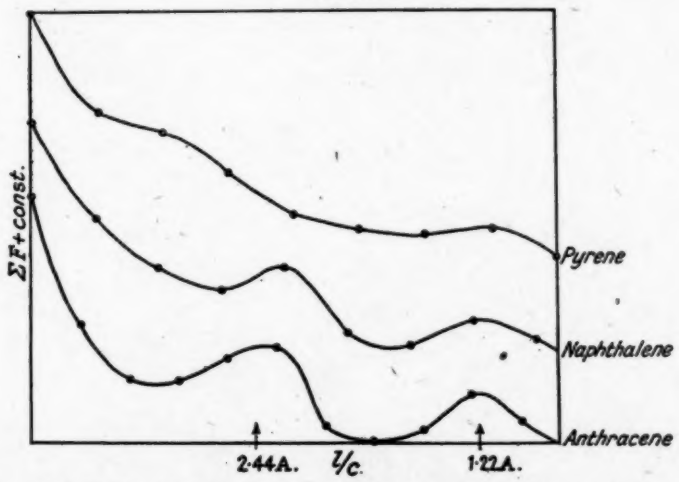
probable arrangements for the molecules in the crystal, but the work does not lead to the determination of any atomic positions.

Analysis of the structure. We may consider the asymmetric crystal unit to consist of one complete molecule, and it is reasonable to assume as a first approximation a regular planar structure in conformity with the chemical evidence. Now, the length of the *b* axis in pyrene is 9·24 A., which is very nearly twice that of coronene (Robertson and White, *loc. cit.*) and of phthalocyanine (Robertson, *J.*, 1935, 615). Both these structures belong to the same space-group, but have only two molecules per unit cell. It therefore seemed a reasonable assumption that in pyrene the molecular planes might have a similar tilt to the *b* axis (about 45°) but with two molecules instead of one accommodated in each *b* translation. These two molecules would be grouped about one crystallographic centre of symmetry.

This enables one orientation angle to be estimated; but to specify completely the position of our molecular model in the crystal, five degrees of freedom remain, *viz.*, two other orientation angles and the co-ordinates (x_p, y_p, z_p) of its centre with respect to the crystallographic origin (centre of symmetry).

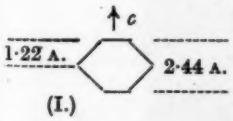
Another clue to the molecular arrangement is provided by the characteristic appearance of the *c* axis rotation photograph (see Plate) and by comparison with naphthalene and anthracene

FIG. 1.



Periodicities in the anthracene, naphthalene, and pyrene structures.

(Robertson, *Proc. Roy. Soc.*, 1933, *A*, **140**, 79; **142**, 674). In pyrene there is a tendency for the third and the fourth layer line ($l = 3$ and $l = 4$) to be enhanced. The naphthalene photograph is similar, while in anthracene the fourth and the fifth layer line ($l = 4$ and $l = 5$) are enhanced. The analysis may be carried further by a study of the general reflections from planes beyond the limits of these photographs, when it is found that in pyrene and in naphthalene planes with $l = 7$, and in anthracene planes with $l = 9$, give enhanced reflections. These results are given more quantitatively in Fig. 1, where ΣF for a selection of planes are plotted against l/c for each crystal. There is clearly an important periodicity at about 1·22 A. on this reciprocal scale in each crystal, and a further periodicity at about 2·44 A. in naphthalene and anthracene, but this latter periodicity is much less defined in pyrene.



(I.)

Now, the width of a benzene ring of radius 1·41 A. is 2·44 A., and the half width is 1·22 A. It may therefore be inferred that the arrangement of the rings in these crystals is such that the above periodicities coincide at least approximately with the direction of the *c* axis in each case, as indicated in (I).

This correlation has been confirmed in the case of naphthalene and anthracene by detailed structure analysis (Robertson, *loc. cit.*). In pyrene we may expect a less exact alinement, and the condensed four-membered ring system will further suppress the 2·44 A. periodicity.

The remaining degrees of freedom can be determined with considerable precision from a survey of certain (*h*0*l*) structure factors for small spacing planes. Absolute measurements show

FIG. 2*a*.

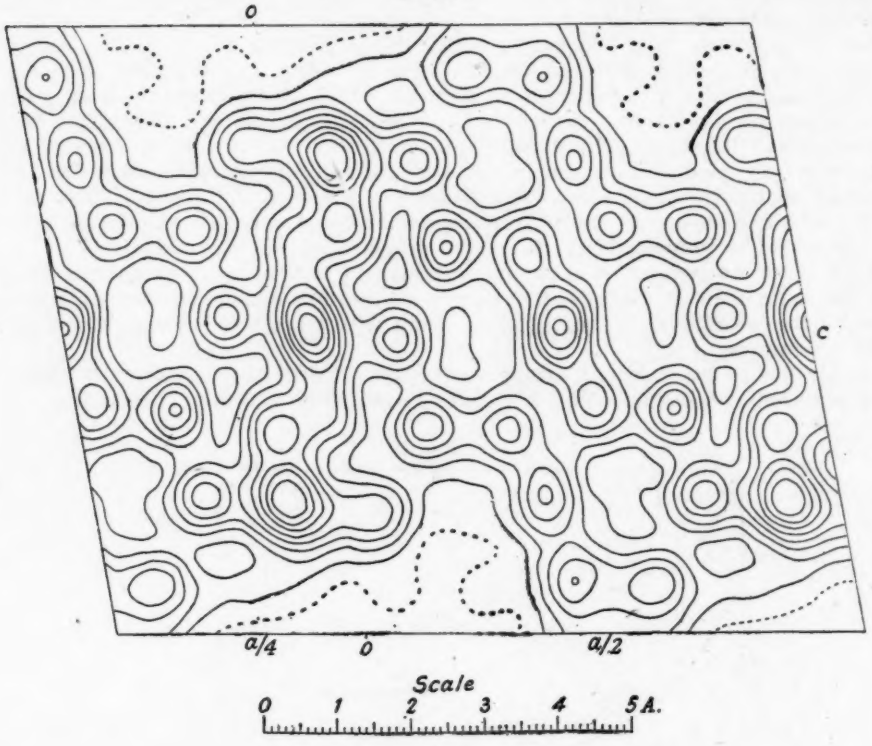
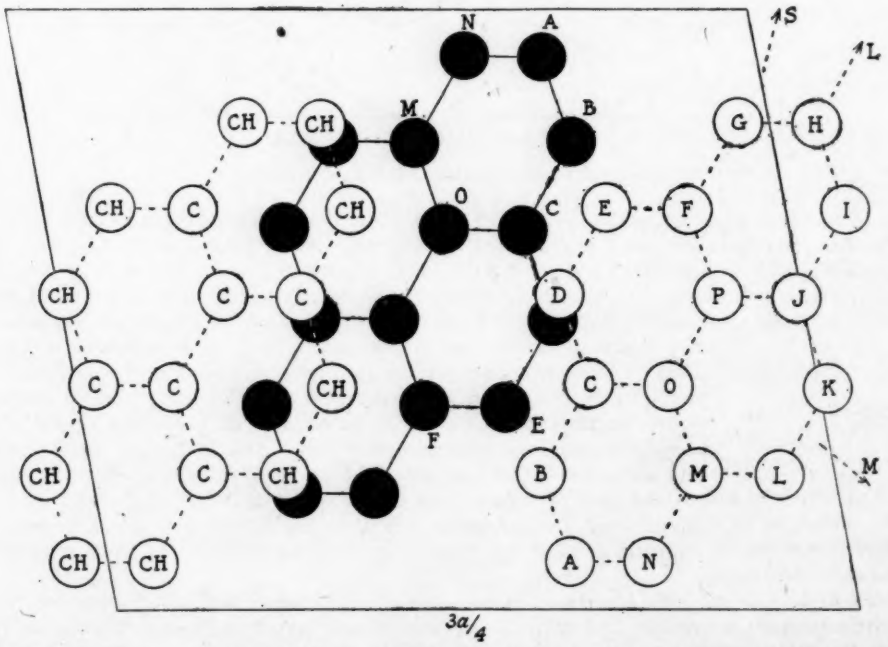


FIG. 2*b*.



Projection along the* b *axis, on the* (010) *plane. The overlapping molecules are inclined at about 40° to the projection plane, the molecular direction* S *lying in the projection plane. Each contour line corresponds to one electron per* A.^{2}, *the one-electron line being dotted.

FIG. 3*a*.

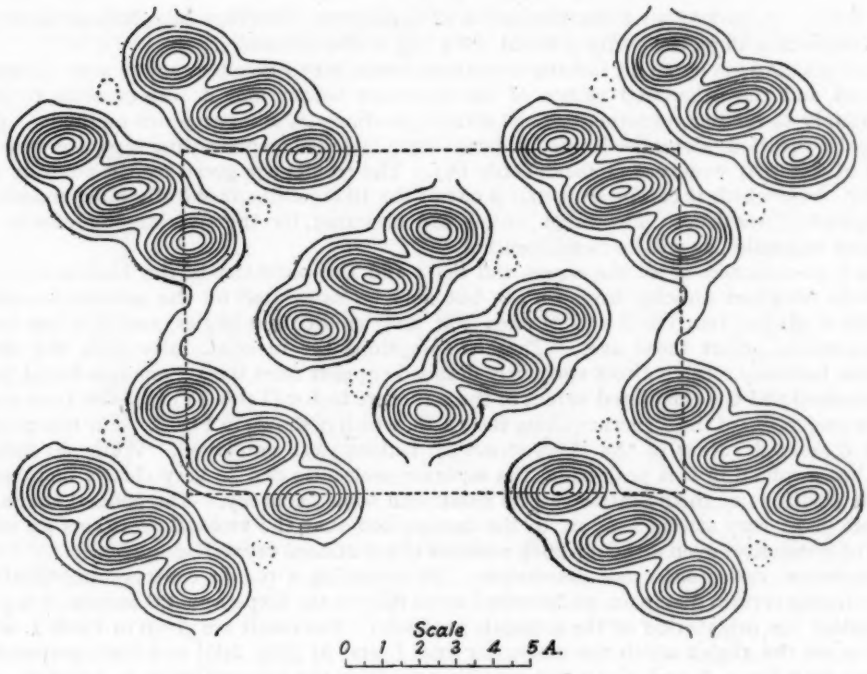
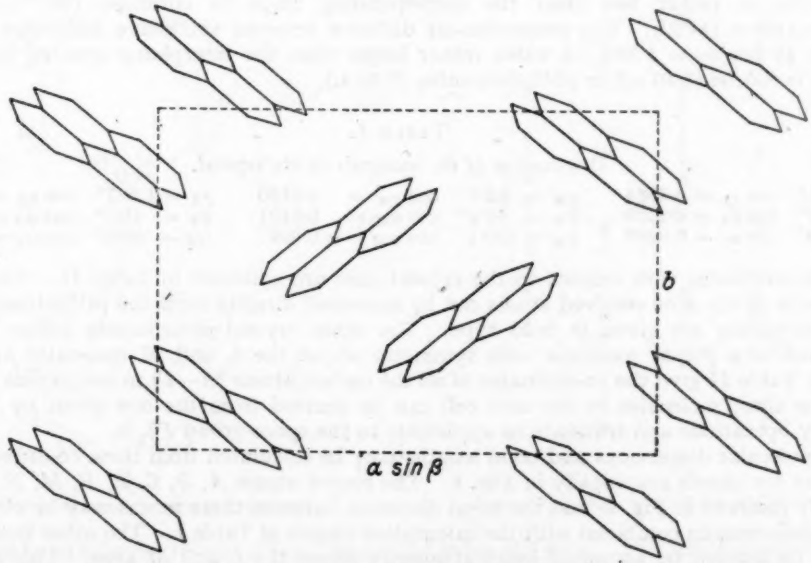


FIG. 3*b*.



Normal projection along the c *axis, showing the relative positions of* 10 *molecules. Contour scale as in Fig.* 1.

that for the (007), (206), (403), (80$\bar{1}$), (12,0$\bar{6}$), and (12,01) and (12,02) planes the contributions of many of the atoms must be in phase. A diagram similar to that given for coronene (Robertson and White, *loc. cit.*, Fig. 1) can be constructed, from which it is found that only one orientation of the proposed model will satisfy the conditions.

Other outstanding features of the spectra are the almost complete quarterings of the (h00)

and $(0k0)$ series of reflections. This serves to fix the molecular centres at approximately $\frac{a}{8}$, $\frac{b}{8}$ ($x_p = 1{\cdot}70$ A., $y_p = 1{\cdot}16$ A.) from the centre of symmetry. Further calculations show that a small translation along the c axis of about 0·5 A. (z_p) is also necessary.

Trial calculations based on the above considerations led to excellent agreements between the measured and the calculated values of the structure factor, and it was possible to proceed immediately to further refinement of the atomic positions by Fourier series methods. For the principal projection, along the b axis, 50 terms were included, representing separately measured values of the $(h0l)$ structure factors (Table IV). The results are given by the contour map of Fig. 2(a), from which it can be seen that 9 out of the 16 crystallographically independent atoms are separately resolved. The other atoms are obscured by the overlapping effects of the adjoining molecules, as will be clear from Fig. 2(b).

The y co-ordinates of all the atoms and the x and z co-ordinates of the 7 unresolved atoms cannot be obtained directly from Fig. 2, but may be calculated on the assumption that the molecule is planar, that the L and M axes [Fig. 2(b)] are at right angles, and that the molecule is symmetrical about these axes. These assumptions are in conformity with the chemical evidence, but they receive direct and fairly detailed support from the agreements found between the measured and the calculated values of the structure factor (Table IV) and also from a second Fourier projection of the structure along the c axis, which is shown in Fig. 3. For this projection the 36 measured values of the $(hk0)$ structure factors were employed. While no individual atoms are resolved in this projection, the separate molecules can be very clearly distinguished, and the positions of their centres can be fixed with some accuracy. The general shape of the contours gives very strong support to the assumption that the molecule contains an inherent centre of symmetry, even although such a centre is not utilised crystallographically.

Orientation, co-ordinates and dimensions. By assuming a planar centrosymmetrical model and averaging certain distances, as described more fully in the Experimental section, it is possible to calculate the orientation of the molecule precisely. The result are given in Table I, where χ, ψ, and ω are the angles which the molecular axes L and M [Fig. 2(b)] and their perpendicular, N, make with the a, b, and c' crystallographic axes (c' is the perpendicular to a and b). These results show that the inclination of the molecular plane to the (010) plane, expressed by ψ_N, is 40·2°. This is rather less than the corresponding angle in coronene (43·7°) or in the phthalocyanines (44·2°). The perpendicular distance between successive molecular planes is given by $\frac{1}{2}b \cos \psi_N = 3{\cdot}53$ A., a value rather larger than the interplanar spacing in graphite (3·41 A.), coronene (3·40 A.), or phthalocyanine (3·38 A.).

TABLE I.

Orientation of the molecule in the crystal.

$\chi_L = 61{\cdot}1°$	$\cos \chi_L = 0{\cdot}4834$	$\chi_M = 52{\cdot}2°$	$\cos \chi_M = 0{\cdot}6130$	$\chi_N = 128{\cdot}7°$	$\cos \chi_N = -0{\cdot}6248$
$\psi_L = 77{\cdot}7°$	$\cos \psi_L = 0{\cdot}2130$	$\psi_M = 52{\cdot}4°$	$\cos \psi_M = 0{\cdot}6101$	$\psi_N = 40{\cdot}2°$	$\cos \psi_N = 0{\cdot}7630$
$\omega_L = 31{\cdot}9°$	$\cos \omega_L = 0{\cdot}8487$	$\omega_M = 120{\cdot}1°$	$\cos \omega_M = -0{\cdot}5017$	$\omega_N = 80{\cdot}5°$	$\cos \omega_N = 0{\cdot}1648$

The co-ordinates with respect to the crystal axes are collected in Table II. The x and z co-ordinates of the nine resolved atoms can be measured directly from the projection in Fig. 2, and these values are given in bold type. The other crystal co-ordinates follow from the assumption of a planar molecule with symmetry about the L and M molecular axes. The figures in Table II give the co-ordinates of all the carbon atoms (A—P) in one pyrene molecule. The other three molecules in the unit cell can be derived from the one given by the usual symmetry operations and translations applicable to the space-group $P2_1/a$.

The molecular dimensions and bond lengths may be calculated from these co-ordinates, and the results are shown graphically in Fig. 4. The ringed atoms A, B, C, E, F, M, N, O, P are separately resolved in Fig. 2, and the bond distances between these atoms may be obtained by direct measurements combined with the orientation angles of Table I. The other bond lengths can only be derived by assuming exact symmetry about the L and M axes. This symmetry may be confirmed by comparing the original direct bond-length measurements of symmetrically placed pairs of resolved atoms. The results are

$AN = 1{\cdot}40$	$AB = 1{\cdot}38$	Assumed mean value, 1·39 A.
$NM = 1{\cdot}43$	$BC = 1{\cdot}42$	,, ,, ,, 1·42 A.
$MO = 1{\cdot}38$	$CO = 1{\cdot}42$	,, ,, ,, 1·39 A.
$PF = 1{\cdot}38$	$CO = 1{\cdot}42$	,, ,, ,, 1·39 A.

The deviations from the mean values are nowhere greater than 0·03 A., and we do not feel that

TABLE II.

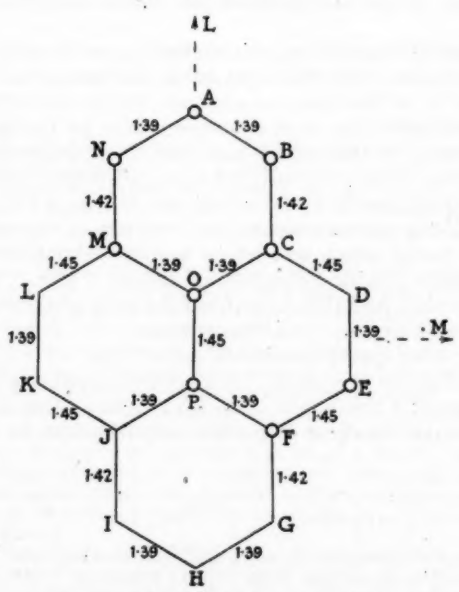
Co-ordinates. Centre of symmetry as origin. x, y, z, are referred to the monoclinic crystal axes. x', y, z', are rectangular co-ordinates referred to the a and b crystal axes, and their perpendicular, c'.

$$x = x' - z' \cot \beta; \quad z = z' \operatorname{cosec} \beta.$$

Atoms (cf. Figs. 2 and 4).	x, A.	y, A.	z, A.	x', A.	z', A.	$2\pi x/a$.	$2\pi y/b$.	$2\pi z/c$.
A	**3·85**	−0·41	**3·51**	3·229	3·463	101·9°	− 16·0°	151·0°
B	**4·04**	0·18	**2·31**	3·630	2·271	106·9	7·1	99·4
C	**3·14**	−0·12	**1·08**	2·943	1·065	83·1	− 4·6	46·5
D	3·33	0·49	−0·18	3·364	−0·181	88·1	19·3	− 7·9
E	**2·45**	0·19	**−1·38**	2·692	−1·361	64·9	7·7	− 59·4
F	**1·33**	−0·73	**−1·37**	1·571	−1·345	35·2	− 28·5	− 59·0
G	0·43	−1·03	−2·59	0·884	−2·551	11·4	− 40·2	−111·4
H	−0·65	−1·91	−2·58	−0·189	−2·537	−17·2	− 74·8	−111·0
I	−0·83	−2·50	−1·37	−0·590	−1·345	−22·0	− 97·8	− 59·0
J	0·07	−2·20	−0·14	0·097	−0·139	1·9	− 86·0	− 6·0
K	−0·12	−2·81	1·12	−0·324	1·107	− 3·2	−109·9	48·2
L	0·76	−2·51	2·32	0·348	2·287	20·1	− 98·3	99·8
M	**1·88**	−1·59	**2·31**	1·469	2·271	49·8	− 62·1	99·4
N	**2·78**	−1·29	**3·53**	2·156	3·477	73·6	− 50·5	151·8
O	**2·06**	−1·01	**1·09**	1·870	1·078	54·5	− 39·5	46·9
P	**1·14**	−1·31	**−0·15**	1·170	−0·152	30·2	− 51·2	− 6·5
Centre of mol.	1·604	−1·160	0·470	1·520	0·463	42·5	− 45·3	19·9

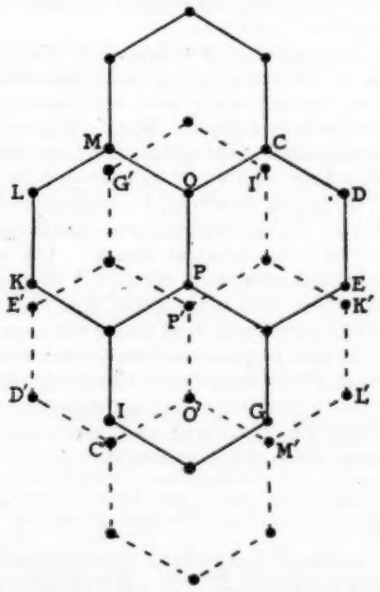
any significance can be attached to these deviations. The mean values have therefore been used in Fig. 4.

FIG. 4.



Dimensions of the pyrene molecule.

FIG. 5.



Normal projection of two parallel molecules.

For the bond lengths OP and EF we obtain the value of 1·45 A. It is unfortunate that these unusually large values cannot be further confirmed by direct measurements on the bonds CD, JK, or LM. From the nature of the projection it is clear that the possible error in the bond lengths is fairly large, and it may easily amount to $\pm$ 0·03 A. However, the balance of the evidence is fairly strong that the bonds OP and EF (directly measured), and probably CD, JK, and LM as well, are distinctly longer than any of the other bonds within the molecule.

With regard to the hexagon angles, there is no evidence that any of these differ appreciably from 120°.

It is convenient to summarise the molecular structure by giving the co-ordinates of the atoms

with reference to the molecular axes L, M, and N. These are collected in Table III. When these figures are combined with the crystal co-ordinates of the molecular centre (x_p', y_p, z_p') and the orientation angles, according to the relations

$$\begin{aligned} x' &= L\cos\chi_L + M\cos\chi_M + N\cos\chi_N + x_p' \\ y &= L\cos\psi_L + M\cos\psi_M + N\cos\psi_N + y_p \\ z' &= L\cos\omega_L + M\cos\omega_M + N\cos\omega_N + z_p' \end{aligned}$$

where $x_p' = 1{\cdot}520$, $y_p = -1{\cdot}160$, $z_p' = 0{\cdot}463$ A., the crystal co-ordinates of Table II are reproduced.

TABLE III.

Co-ordinates with respect to molecular axes.

Atoms.	L, A.	M, A.	N, A.	Atoms.	L, A.	M, A.	N, A.
A, H	±3·535	0	0	*D, E, K, L*	±0·695	±2·459	0
B, G, I, N	±2·840	±1·203	0	*O, P*	±0·725	0	0
C, F, J, M	±1·420	±1·203	0				

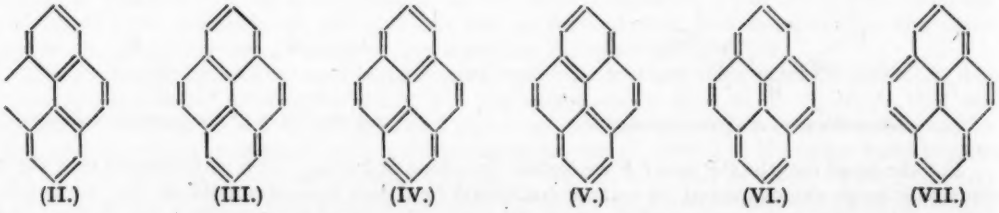
Intermolecular distances. The closest approach of adjacent pyrene molecules occurs along the b axis where the interplanar distance is 3·53 A. Here the molecules are grouped in pairs about the symmetry centres, and the normal projection of one of them in the plane of the other is shown in Fig. 5. The hexagons are clearly arranged so as to avoid any direct overlap. Four pairs of atoms, *PP'*, *MG'*, *CI'*, and *KE'*, are nearly over each other, and for these the approach distance is 3·54 A. The other pairs are in staggered positions at rather greater distances.

From atom D on the standard molecule to atom O' (inverted) on the reflected molecule half a translation along the a axis the distance is 3·61 A., and from D to P' it is 3·64 A. From A on the standard molecule to N' (inverted) on the reflected molecule half a translation along a and one translation along c the distance is 3·96 A. All other intermolecular distances appear to be greater than 4 A.

Discussion of Results.—The bond-length variations in the pyrene molecule, as depicted in Fig. 4, are even greater than those found for coronene. On the other hand, we cannot expect as high an accuracy from the present analysis as from the coronene analysis, for reasons which have been explained. The data given in Fig. 4 represent the most probable values for the bond lengths, after averaging. But as the possible error in individual bond-length measurements may be as high as ± 0·03 or ± 0·04 A., the results must obviously be accepted with caution.

It should, however, be emphasised that the bond-length variations shown in Fig. 4 for the resolved atoms (circled) are based entirely on X-ray measurements, and are not in any way derived from chemical theory. The initial trial model which was set up in order to determine the phase constants consisted of perfectly regular planar hexagons of radius 1·39 A. The final shifts from these initial positions are considerable, and they arise from the measured values of the structure factors which were employed as coefficients in the Fourier series.

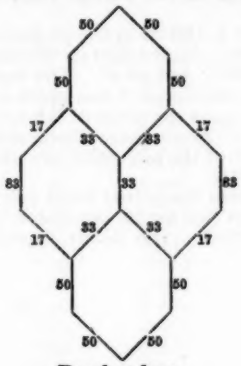
In view of this, the results receive a rather striking qualitative confirmation from a study of the simple valency bond structures which are applicable to pyrene. For a fixed position of the carbon atoms there are six different ways of drawing the bonds, (II)—(VII), and these may perhaps be considered as the structures which make the most important contributions to the normal state of the molecule.



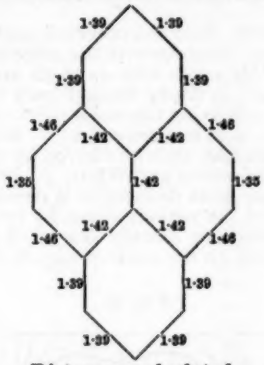
(II.) (III.) (IV.) (V.) (VI.) (VII.)

Assuming in the first instance that these structures make equal contributions (this is unlikely to be true), it is easy to compute the average double-bond character for each link in the molecule. This is shown in (VIII) as percentage double-bond character, and in (IX) these figures are translated into distances on the basis of Pauling and Brockway's empirical curve relating double-bond character and distance (*J. Amer. Chem. Soc.*, 1937, **59**, 1223). In (X) the measured values of Fig. 4 are repeated for convenient comparison.

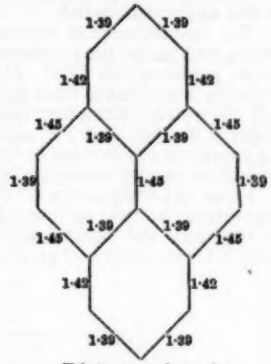
There is a distinct general resemblance between the measured values and those predicted on the basis mentioned above. The largest deviations occur in the central bonds where the



Bond orders.
(VIII.)



Distances calculated.
(IX.)



Distances found.
(X.)

measured values vary from 1·38 to 1·45 A., while the predicted values are constant at 1·42 A. In the upper and the lower ring the predicted values are again more constant than the measured values. The average bond length over the whole molecule is in excellent agreement, the predicted value being 1·408 A. and the measured value 1·412 A.

Chemical evidence appears to suggest that the structures (II)—(V) are those most consistent with the reactivity of pyrene (see, for example, Cook, *Ann. Reports*, 1942, **39**, 163). If the contributions of these structures are increased relatively to the others the main effect on the above calculations is to increase the length of the central bond, in agreement with the observations.

More detailed discussion of the bond distances is probably not justified until more reliable measurements can be made, or until other similar ring structures have been measured.

Experimental.

X-Ray Measurements.—Small tabular crystals, displaying the (001) and (110) faces, were employed. They were mounted for rotations about the *a*, *b*, and *c* crystallographic axes, the weights of the principal specimens employed for intensity measurements being 0·077, 0·048, and 0·147 mg. The dimensions of the specimens were such as to make relative absorption corrections for different reflections in the same zone unnecessary. Absorption corrections were applied, however, in calculating the scale of absolute values of F.

All the *X*-ray work was carried out with copper-$K\alpha$ radiation, $\lambda = 1{\cdot}54$. Rotation, oscillation, and moving-film photographs were taken, the latter mainly for intensity records. The observed halvings led to the space group $P2_1/a$ without ambiguity. The intensity measurements were carried out on a number of calibrated moving-film exposures by means of a photometer of the type described by Robinson (*J. Sci. Instr.*, 1933, **10**, 233), and the different sets were correlated through the common axial reflections. Very strong reflections were reduced by a factor of 12 by means of automatic shutters in order to give accurate comparisons with the weaker reflections.

Absolute measurements were made by comparisons with standard crystals on the two-crystal moving-film spectrometer (Robertson, *Phil. Mag.*, 1934, **18**, 729). In one experiment a small crystal of *i*-erythritol, and in another experiment a small crystal of oxalic acid, were used as standards. (Direct absolute measurements had previously been made on these standards with an ionisation spectrometer.) Good agreements were obtained in the two experiments. The absolute values of F were calculated by the usual formulæ applicable to mosaic-type crystals, and the results are collected in Table IV under "F meas.".

Fourier Analysis.—Using the phase constants determined from the trial structures and the measured values of F, a double Fourier series was set up according to the usual formulæ. For the projection along the *b* crystal axis on the (010) plane, the electron density was computed at 450 points on the asymmetric unit, the *a* axis being divided into 60 parts (intervals of 0·227 A.) and the *c* axis into 30 parts (intervals of 0·279 A.). The summations were carried out by means of 3-figure strips (Robertson, *Phil. Mag.*, 1936, **21**, 176). The positions of the contour lines were obtained by graphical interpolation from the summation totals, by making sections of both the rows and the columns. The resulting contour map is shown in Fig. 2, three-quarters of the unit cell being included.

The projection along the *c* axis (Fig. 3) was computed in a similar manner. In this case each axis was divided into 60 parts, the intervals being 0·154 A. along *b* and 0·223 A. along $a \sin \beta$.

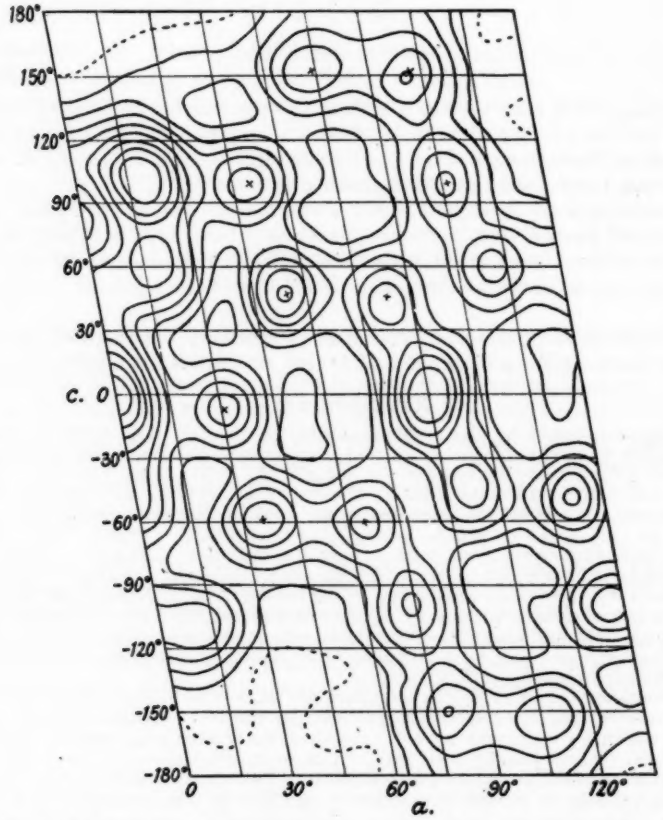
Orientation of the Molecule, and Co-ordinates.—From a consideration of the observed lengths in projection of *ON* and parallel distances [Fig. 2(*b*)], which can be only slightly tilted, it was found that the best average radius of the hexagon was 1·41 A. With this average value and the assumption that the molecule is flat and the axes *L* and *M* are at right angles, it was possible to calculate the orientation of the molecule with regard to the crystallographic axes.

The distances *NB*, *MC*, and *PE* are 1·938 ± 0·030 A. in the projection, hence ψ_M, the angle which *M* makes with the *b* axis, is 52·4°. This method cannot be used to find the tilt of *L* as the line lies so nearly in the projection plane that a small discrepancy in the observed value would lead to a large difference in the angle calculated.

The calculation can be made, however, from the observed angle between *L* and *M* in the projection. Let η_L and η_M be the angles which *L* and *M* make with the *a* axis in projection. η_L is taken as the mean of the angles which *BCF*, *AOP*, and *NM* make with *a*, which are 60·2°, 60·0°, and 61·3°. The last is probably less reliable than the others as it is drawn through only two atoms and hence it was given only half the weight of the first two angles in deriving the mean value of 60·34°. η_M is the mean of the angles which *NB*, *MC*, and *PE* make with *a*, and is observed as − 39·3° ± 0·4°. From these observations the complete orientation of the molecule may then be derived by making use of the nine relations which were given in the coronene analysis (Robertson and White, *J.*, 1945, 607, 615).

From the orientation of the molecule thus deduced it is possible to obtain the actual bond lengths connecting the best estimated centres of the various atoms by reducing each line for its calculated tilt. In this way the bond-length determinations already discussed were reached. The finally accepted centres for the resolved atoms are plotted on the contour map in Fig. 6.

FIG. 6.



Co-ordinates assigned to the resolved atoms in the pyrene b *axis projection.*

Table II gives the finally accepted co-ordinates for the atoms, and includes the co-ordinates of the centre of the molecule (x_p, y_p, z_p). The latter position can be estimated with considerable accuracy from the *b* axis projection (Fig. 2) and with rather less certainty from the *c* axis projection (Fig. 3). Even on the assumption of a strictly planar molecule, the *b* axis projection gives no information concerning the value of y_p, as the molecules may be translated up or down the *b* axis. The best value of y_p was therefore found by calculations of the (*hk*0) structure-factors, and confirmed from the *c* axis projection (Fig. 3).

On the basis of the final co-ordinates the structure factors were re-calculated and the results are given in Table IV under " F calc.". The scattering curve formerly given for hydrocarbons (Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 110) was found rather unsuitable for pyrene, and the f_e values given below (max. f_e = 100) were used instead.

sin θ (λ = 1·54)	0·1	0·2	0·3	0·4	0·5	0·6	0·7	0·8	0·9
f_e	70	56	43	30	19	12·5	8·5	5	3·5

TABLE IV.

Measured and calculated values of the structure factor.

hkl.	$\sin\theta$ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.	*hkl.*	$\sin\theta$ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.
200	0·115	7·5	+ 7	$20\bar{5}$	0·462	2·5	− 12
400	0·230	47	+ 46	$20\bar{4}$	0·370	19·5	+ 21
600	0·345	< 2	− 4	$20\bar{3}$	0·285	15·5	+ 16
800	0·460	3	− 6	$20\bar{2}$	0·202	40·5	− 35
10,00	0·575	< 3	− 1	$20\bar{1}$	0·135	48	+ 43
12,00	0·690	< 3	− 1	201	0·160	6·5	+ 6
14,00	0·805	4·5	+ 2	202	0·235	18	− 15
020	0·167	< 1·5	+ 2	203	0·320	22	+ 25
040	0·333	19	+ 23	204	0·409	7	+ 1
060	0·500	< 3	+ 1	205	0·500	10·5	− 12
080	0·667	3·5	+ 5	206	0·591	21·5	+ 24
0,10,0	0·833	< 3	0	207	0·683	6·5	+ 6
001	0·094	65	+ 66	208	0·775	< 3	+ 1
002	0·187	32·5	− 31	209	0·868	< 3	0
003	0·281	5	+ 6	$40\bar{8}$	0·743	< 3	+ 3
004	0·374	< 2	− 2	$40\bar{7}$	0·657	< 3	+ 8
005	0·468	< 2·5	− 3	$40\bar{6}$	0·567	< 3	+ 2
006	0·561	9·5	+ 14	$40\bar{5}$	0·484	6·5	+ 4
007	0·654	33	+ 33	$40\bar{4}$	0·403	< 3	− 2
008	0·748	4·5	+ 1	$40\bar{3}$	0·330	3	− 7
009	0·841	4	− 4	$40\bar{2}$	0·270	12·5	+ 19
				$40\bar{1}$	0·233	38	+ 32
011	0·125	13	+ 12	401	0·264	20·5	− 16
012	0·205	< 5	− 4	402	0·320	27·5	+ 29
013	0·293	9	+ 9	403	0·393	40·5	+ 40
014	0·383	10·5	− 11	404	0·472	< 3	+ 1
015	0·475	< 8	+ 7	405	0·555	< 3	0
016	0·567	< 9	− 9	406	0·641	< 3	+ 3
017	0·660	11	− 13	407	0·729	< 3	+ 3
018	0·752	<10	+ 1	408	0·820	< 3	− 2
021	0·191	< 5	− 2	$60\bar{8}$	0·767	< 3	0
022	0·251	8·5	+ 7	$60\bar{7}$	0·685	< 3	+ 2
023	0·326	26·5	− 25	$60\bar{6}$	0·605	< 3	+ 4
024	0·409	24	− 14	$60\bar{5}$	0·531	17	− 14
025	0·496	< 8	+ 7	$60\bar{4}$	0·461	17	− 14
026	0·585	< 9	− 3	$60\bar{3}$	0·405	< 3	− 1
027	0·675	<10	− 1	$60\bar{2}$	0·362	3·5	− 5
031	0·267	< 6	− 1	$60\bar{1}$	0·342	9·5	− 11
032	0·312	11·5	+ 10	601	0·373	< 2	− 1
033	0·376	35	+ 30	602	0·421	17·5	− 13
034	0·450	12	− 12	603	0·482	9	− 9
035	0·530	< 9	0	604	0·550	< 3	+ 1
036	0·614	<10	+ 4	605	0·625	< 3	− 3
037	0·701	<10	+ 2	606	0·707	< 3	− 3
041	0·346	9	+ 14	607	0·790	< 3	− 1
042	0·382	13·5	− 15	608	0·875	< 3	+ 1
043	0·436	6·5	− 6	$80\bar{9}$	0·885	4	+ 4
044	0·501	< 9	− 3	$80\bar{8}$	0·806	5	+ 10
045	0·574	< 9	+ 2	$80\bar{7}$	0·732	< 3	+ 1
046	0·652	<10	+ 2	$80\bar{6}$	0·660	< 3	+ 3
047	0·734	<10	+ 4	$80\bar{5}$	0·595	< 3	+ 6
051	0·427	10·5	− 7	$80\bar{4}$	0·540	< 3	+ 2
052	0·457	< 8	− 4	$80\bar{3}$	0·494	< 3	+ 3
053	0·502	< 9	+ 3	$80\bar{2}$	0·466	23·5	+ 20
054	0·560	< 9	− 7	$80\bar{1}$	0·455	35	+ 31
055	0·626	<10	+ 3	801	0·486	< 3	+ 4
056	0·698	<10	+ 3	802	0·528	9	+ 12
061	0·509	7·5	− 5	803	0·580	5·5	+ 6
062	0·534	< 9	− 3	804	0·641	< 3	0
063	0·574	< 9	− 5	805	0·710	< 3	− 2
071	0·591	9	+ 9	806	0·785	< 3	+ 2
072	0·613	<10	+ 2	$10,0\bar{6}$	0·730	< 3	− 1
073	0·647	<10	+ 6	$10,0\bar{5}$	0·675	3	+ 10
				$10,0\bar{4}$	0·630	< 3	− 2
$20\bar{9}$	0·830	< 3	− 2	$10,0\bar{3}$	0·593	< 3	− 6
$20\bar{8}$	0·737	< 3	− 1	$10,0\bar{2}$	0·574	22	+ 17
$20\bar{7}$	0·647	7	− 7	$10,0\bar{1}$	0·569	< 3	− 2
$20\bar{6}$	0·552	< 3	+ 5	10,01	0·600	< 3	0

TABLE IV.—*continued.*

Measured and calculated values of the structure factor.

hkl.	sin θ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.	*hkl.*	sin θ ($\lambda = 1{\cdot}54$).	F, meas.	F, calc.
10,02	0·637	< 3	+ 3	360	0·529	2·5	− 4
10,03	0·683	< 3	− 3	370	0·608	< 3	− 3
10,04	0·738	< 3	0	380	0·689	< 3	0
10,05	0·802	5·5	+ 7	410	0·245	11	− 10
10,06	0·870	< 3	− 3	420	0·284	< 3	+ 5
12,07	0·865	< 3	− 3	430	0·340	20	+ 20
12,06	0·809	14	+ 14	440	0·405	30·5	+ 30
12,05	0·764	10·5	+ 13	450	0·476	9	+ 7
12,04	0·725	< 3	− 2	460	0·551	< 3	− 1
12,03	0·698	< 3	0	470	0·627	< 3	− 2
12,02	0·682	< 3	0	480	0·705	< 3	+ 2
12,01	0·682	< 3	− 2	510	0·300	10	− 11
12,01	0·715	27	+ 28	520	0·333	7·5	− 6
12,02	0·749	18	+ 16	530	0·381	< 3	+ 1
12,03	0·792	< 3	− 4	540	0·440	10·5	+ 8
12,04	0·840	< 3	0	550	0·506	< 3	0
12,05	0·885	< 2	0	560	0·577	3	− 4
14,07	0·944	< 2	0	570	0·650	< 3	+ 3
14,06	0·897	4·5	− 4	610	0·355	10	− 11
14,05	0·856	4	− 1	620	0·383	15	− 14
14,04	0·828	< 3	− 1	630	0·426	< 3	+ 3
14,03	0·806	< 3	− 1	640	0·480	< 3	− 1
14,02	0·795	< 3	+ 3	650	0·541	5	− 5
14,01	0·798	< 3	− 4	660	0·607	< 3	+ 3
14,01	0·830	4	+ 3	710	0·411	< 3	+ 4
14,02	0·861	< 3	0	720	0·436	< 3	+ 4
14,03	0·898	< 2·5	0	730	0·474	< 3	+ 4
14,04	0·943	< 2	− 1	740	0·523	< 3	− 1
				750	0·580	< 3	+ 2
110	0·102	43	+ 46	760	0·642	4	− 7
120	0·176	42	+ 45	770	0·709	< 3	− 4
130	0·257	12·5	− 21	780	0·778	< 3	− 2
140	0·338	14·5	− 10	810	0·468	< 3	− 2
150	0·421	21·5	− 22	820	0·490	< 3	+ 1
160	0·503	15	− 14	830	0·524	< 3	+ 2
170	0·586	6	+ 6	840	0·568	< 3	− 4
180	0·669	< 3	0	850	0·621	< 3	+ 1
210	0·142	42	+ 43	860	0·679	< 3	− 1
220	0·203	83	−107	910	0·524	< 3	− 3
230	0·275	32·5	+ 33	920	0·544	< 3	− 1
240	0·353	2	− 3	930	0·575	< 3	− 1
250	0·432	17	− 18	940	0·616	< 3	− 4
260	0·513	17	− 18	950	0·665	< 3	0
270	0·594	3·5	− 4	10,10	0·581	< 3	+ 1
280	0·677	< 3	0	10,20	0·599	3	+ 6
310	0·192	26·5	− 22	10,30	0·627	< 3	− 1
320	0·240	35·5	+ 32	10,40	0·665	< 3	− 1
330	0·304	22	+ 23	11,10	0·638	< 3	0
340	0·375	17·5	+ 13	11,20	0·654	< 3	+ 4
350	0·451	6·5	− 6	11,30	0·680	< 3	+ 3

These are generally smaller than the previous values. This may be due in part to errors in the absolute scale, but in addition there is a definite tendency for pyrene reflections of high order to fall off in intensity more rapidly than in anthracene and other hydrocarbons. This points to a curious difference in temperature factor, or possibly to some randomness in the structure, but further measurements are required before definite conclusions can be drawn.

The general agreements are very good, the average discrepancies, expressed as a sum of all the discrepancies divided by the sum of the measured F values, being 14·3% for the (*h*0*l*), 12·9% for the (*hk*0), and 8·8% for the (0*kl*) structure factors, and 12·6% for all the structure factors together.

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[*Received, July 1st,* 1946.]

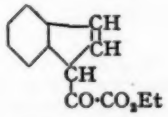
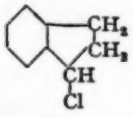
73. *The Isolation of Indene from Heavy Naphthas.*

By Robert D. Haworth, C. Lindley, and D. Woodcock.

Two new methods, based on the formation of ethyl indenyl-1-glyoxylate and 1-chlorohydrindene respectively, have been developed for the recovery of high-quality indene from commercial naphthas.

Published methods for the isolation of indene from heavy naphtha fractions include (*a*) crystallisation of the picrate and subsequent decomposition with steam (Krämer and Spilker, *Ber.*, 1890, **23**, 3276), (*b*) formation of sodioindene by means of sodamide, followed by steam decomposition (Weissgerber, *Ber.*, 1909, **42**, 569; D.R.-PP. 205,465, 209,694), (*c*) azeotropic distillation (U.S.PP. 2,279,778, 2,279,779, 2,279,780). Each of these has certain disadvantages and the two new methods now reported may prove more economical and convenient.

Condensation of indene with ethyl oxalate in alcoholic solution in the presence of sodium ethoxide (Wislicenus, *Ber.*, 1900, **33**, 773; Thiele, *ibid.*, p. 851) yields ethyl indenyl-1-glyoxylate, (I) m. p. 89—90°, which may be removed from the heavy naphtha residue by utilising its solubility in sodium hydroxide solution. Optimum conditions for the recovery of the indene from the sodio-derivative of (I) have been examined, and unless very pure indene is desired, it is unnecessary, and indeed unprofitable, to isolate the ester (I) from the reaction mixture.

(I.)   (II.)

Indene absorbs hydrogen chloride with the formation of 1-chlorohydrindene (II) (Weissgerber and Brehme, *Ber.*, 1911, **44**, 1436; Courtot and Dordelinger, *Compt. rend.*, 1924, **179**, 1168) which boils some 30° higher than indene, and forms the basis of the second method for the separation of pure indene from commercial naphthas.

Experimental.

Ethyl Indenyl-1-glyoxalate (I).—Steam-distilled and dried indene (10 g., s. p. — 1·8°) was added with shaking and water-cooling to a solution of ethyl oxalate (12 g.) in absolute alcohol (40 c.c.) in which sodium (2 g.) had been dissolved. After 0·25 hour, the orange-coloured solution was poured into water (500 c.c.), neutral matter removed in ether, and the aqueous layer acidified with concentrated hydrochloric acid. The orange-yellow precipitate was extracted with ether, the extract dried, and the solvent removed. The residue crystallised from benzene in orange-yellow rhombs (8·4 g.), m. p. 89—90°, unchanged by further recrystallisations from the same solvent (Wislicenus, *loc. cit.*, gives m. p. *ca.* 80°).

Recovery of Indene from the Above Ester.—The ester (I) (20 g.) was dissolved in 20% sodium hydroxide (120 c.c., *ca.* 6 mols.) and after 3 hours at room temperature the solution was distilled in steam for 2—3 hours. The distillate was extracted with ether, the extract dried, and the solvent removed through a short column. Distillation of the residue gave indene (7·5 g.), b. p. 74—75°/16 mm., s. p. — 1·7°.

Recovery of Indene from Heavy Naphtha by Ethyl Oxalate Method.—The following represents a typical experiment. Steam-distilled and dried heavy naphtha (14·4 c.c. containing 69% of indene, estimated by the method of Weger and Bilman, *Ber.*, 1903, **36**, 640) was added with shaking and cooling to a solution of ethyl oxalate (12·4 g.) in ethyl alcohol (40 c.c.) containing sodium (2·0 g.). After 0·25 hour, water was added, neutral impurities removed in ether,* and solid sodium hydroxide (110 g.) added with cooling to the aqueous layer (450 c.c.). After 3 hours at room temperature the solution was steam-distilled, and the indene (6·8 g.), b. p. 72—74°/17 mm., s. p. — 2·20°, was isolated from the distillate by ether extraction.

When the indene content of the heavy naphtha is low (*e.g.*, 10—50%) the inert alkali-insoluble oil can be separated and the ether extraction at this stage becomes unnecessary.

The results from a selection of experiments included in Table I indicate that indene of high purity can be obtained in 65% yield from heavy naphtha fractions originally containing 10—100% of indene.

Recovery of Indene from Heavy Naphtha by Hydrogen Chloride Method.—Naphtha (100 g., washed with alkali and acid) was saturated with dry hydrogen chloride at — 5° to — 10° (not critical), and after 3 hours, excess was removed in a stream of air. The residue was fractionated at 2 mm. (12 mm. has also been used) from an oil-bath, a glass spiral column 7″ long being used. The batch was kept at 95° until most of the non-indene fraction, b. p. 55—79°/2 mm., which may be profitably refractionated, was obtained. Distillation of the residue yielded 1-chlorohydrindene, b. p. 79—81°/2 mm., but this operation was usually omitted and the total residual oil was refluxed with anhydrous sodium carbonate (0·7 part) for 0·7 hour, in an oil-bath at 160—170°. The indene was recovered by steam distillation, dried, and distilled.

The copious evolution of hydrogen chloride observed on warming 1-chlorohydrindene with sodium carbonate suggests that decomposition occurs in the vapour phase, but some basic substance must be

* Unless the naphtha was subjected to a preliminary steam-distillation, which removed traces of polymeric and oxidation products, objectionable emulsions were obtained at this stage.

TABLE I.

Recovery of indene from heavy naphthas.

Source of indene.	S. p.	Purity, %.	S. p. of indene recovered.	Purity, %, of indene recovered.	Recovery, %.
1. Special close-up naphtha fraction from Dorman Long & Co.; b. p. 180—182°	−17·7°	69	−2·2°	97·5	68
2. Dorman Long & Co.'s naphtha; b. p. 175—182°	−26·0	55	−2·4	97·0	67
3. Synthetic mixture containing pure indene and indene-free naphtha	—	11	−3·3	96·0	67

present in order to inhibit the acid-catalysed liquid-phase polymerisation of the indene. Experiments with sodium hydroxide, lime, pyridine, and diethanolamine instead of sodium carbonate have given inferior results.

Typical results with five naphtha samples (each 100 g.) given in Table II show that this method is satisfactory in the case of heavy naphthas supplied by Dorman Long and Co. and the Consett Iron Co., but that it fails with certain naphthas. The failures were first thought to be due to the presence of coumarone in the naphtha, but it was shown that, although this compound absorbs dry hydrogen chloride, yet the gas is completely eliminated by air aspiration. It is probable that the failures are due to the presence of unidentified, unsaturated compounds which combine with hydrogen chloride to form addition compounds inseparable from 1-chlorohydrindene by distillation.

TABLE II.

Source of naphtha.	Purity, %.	Yield of residual oil (A), %.	Yield of recovered indene, %.	S. p. of recovered indene.	Purity, %, of recovered indene.	Recovery of indene, %.
a. Dorman Long & Co.	66	90·8	49·2	− 2·6°	98·5	73
a'. ,, ,, ,, ...	66	84·3	47·9	− 2·5	99	72
b. ,, ,, ,, ...	55	64·4	39·7	− 4·0	96	69
b'. ,, ,, ,, ...	55	69·7	38·3	− 4·1	96	67
c. Consett Iron Co.	38	50·5	27·3	− 3·3	97	70
d. Gas Light & Coke Co.	27	24·0	12·7	−14·5	76	36
d'. ,, ,, ,, ...	27	20·0	11·0	−13·6	78	31
e. Birchenwood Coal & Coke Co.	17	30·0	17·6	−11·0	83	86

Our thanks are due to the Director General of Scientific Research (Defence) for permission to publish this communication.

THE UNIVERSITY, SHEFFIELD, 10. [*Received, July 3rd,* 1946.]

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74. *Pyrazine Derivatives. Part I. 2-Hydroxy-3 : 6-dimethylpyrazine.*

By R. A. BAXTER, G. T. NEWBOLD, and F. S. SPRING.

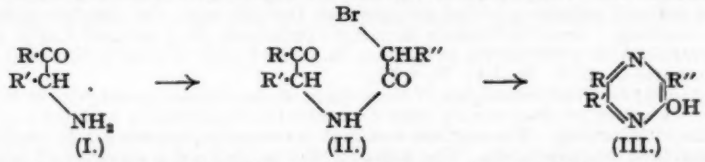
A synthesis of 2-hydroxy-3 : 6-dimethylpyrazine (VII) is described in which *2-aminopropaldehyde diethylmercaptal* (V) is condensed with 2-bromopropionyl bromide to give 2-(*2-bromopropionamido*)*propaldehyde diethylmercaptal* (VI) which, when treated with mercuric chloride in the presence of cadmium carbonate and then with ammonia, gave the required hydroxypyrazine.

Treatment of aminopyrazine and of 2-amino-3 : 6-dimethylpyrazine with nitrous acid gave hydroxypyrazine and 2-hydroxy-3 : 6-dimethylpyrazine respectively.

AN examination of methods for the synthesis of 2-hydroxypyrazines was undertaken with the object of synthesising deoxyaspergillic acid (see Part II, following paper). When this study commenced, two methods for the synthesis of hydroxyalkylpyrazines had been reported. The first, due to Gastaldi (*Gazzetta*, 1921, **51**, I, 233), consisted in the treatment of *iso*nitrosoacetone with sodium bisulphite followed by reaction of the product with potassium cyanide to yield 2 : 5-dicyano-3 : 6-dimethylpyrazine which was converted into 2-hydroxy-3 : 6-dimethylpyrazine-5-carboxylic acid and thence into 2-hydroxy-3 : 6-dimethylpyrazine; this method will be discussed more fully in a later paper.

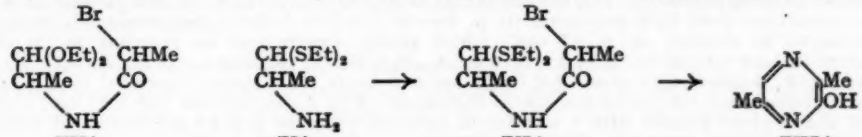
The second route is one described by Tota and Elderfield (*J. Org. Chem.*, 1942, **7**, 317) who developed a method for the condensation of the hydrochloride of an α-amino-ketone (I) with a 2-bromo-substituted acid halide to give, in poor yield, the corresponding 2-bromoacylamido-ketone (II) which on treatment with ammonia gave the hydroxyprazine (III), the last stage

involving the oxidation common to most pyrazine syntheses. Modification of the method to lead to the formation of a 2-hydroxy-3 : 6-dialkylpyrazine would involve the use of the



(I.) (II.) (III.)

hydrochloride of a 2-amino-aldehyde instead of an α-amino-ketone hydrochloride. The hydrochloride of 2-aminopropaldehyde was prepared by Fischer and Kametaka (*Annalen*, 1909, **365**, 7; Neuberg, *Ber.*, 1908, **41**, 956) who described it as a nearly colourless gum which could not be crystallised. We also were unable to crystallise this resin-like salt. Unsuccessful attempts were made to condense the resinous hydrochloride with 2-bromopropionyl bromide. In consequence of this unpromising result, the method was modified, the aldehyde group being protected during the condensation. This modification proved successful, condensation of 2-aminopropaldehyde diethylacetal (Burtles, Pyman, and Roylance, *J.*, 1925, **127**, 585) with 2-bromopropionyl bromide giving 2-(2-*bromopropionamido*)*propaldehyde diethylacetal* (IV) in



(IV.) (V.) (VI.) (VII.)

good yield. We were unable, in spite of many variations in reaction conditions, successfully to hydrolyse the acetal to the required bromo-aldehyde. Likewise, attempts to convert the acetal (IV) directly into 2-hydroxy-3 : 6-dimethylpyrazine failed. This failure we attribute to the difficulty of hydrolysis of the acetal group; when conditions were sufficiently drastic to accomplish this hydrolysis, cleavage of the amide linkage apparently occurred.

An alternative method for the protection of the aldehyde group was next examined in which use was made of an observation that mercaptals can be hydrolysed to the corresponding aldehyde by treatment with mercuric chloride in the presence of an insoluble carbonate (Levene and Meyer, *J. Biol. Chem.*, 1926, **69**, 175; 1927, **74**, 695; Wolfrom, *J. Amer. Chem. Soc.*, 1929, **51**, 2188; cf. Fischer, *Ber.*, 1894, **27**, 673). Treatment of 2-aminopropaldehyde diethylacetal with hydrochloric acid and ethylthiol gave 2-*aminopropaldehyde diethylmercaptal* (V), which reacted smoothly with 2-bromopropionyl bromide to give 2-(2-*bromopropionamido*)*propaldehyde diethylmercaptal* (VI). Treatment of the latter with mercuric chloride in the presence of cadmium carbonate, followed by treatment of the product with ammonia, gave the required 2-hydroxy-3 : 6-dimethylpyrazine (VII), characterised by the preparation of its *picrate*.

Another possible route to hydroxypyrazines was examined simultaneously. It consists in the preparation of an aminopyrazine and treatment of this with nitrous acid. By using this method, aminopyrazine was converted into hydroxypyrazine in 30% yield, and 2-amino-3 : 6-dimethylpyrazine into 2-hydroxy-3 : 6-dimethylpyrazine in 60% yield. Since this work was completed, Weijlard, Tishler, and Erickson (*J. Amer. Chem. Soc.*, 1945, **67**, 802) have prepared hydroxypyrazine by decarboxylation of 2-hydroxypyrazine-3-carboxylic acid, and more recently Erickson and Spoerri (*ibid.*, 1946, **68**, 400) obtained the same compound by treatment of aminopyrazine with nitrosylsulphuric acid.

Experimental.

(M. p.'s are uncorrected.)

2-(2-*Bromopropionamido*)*propaldehyde Diethylacetal*.—2-Bromopropaldehyde diethylacetal was prepared from propaldehyde by using an adaptation of Kuhn and Grundmann's method (*Ber.*, 1937, **70**, 1894) for the preparation of 2-bromo-*n*-valeraldehyde diethylacetal. This method is superior to that employed by Stoermer (*Annalen*, 1900, **312**, 271) and by Burtles, Pyman, and Roylance (*J.*, 1927, 581) and represents a marked improvement over that used by Dworzak and Pfifferling (*Monatsh.*, 1927, **48**, 251) starting from propaldehyde trimer but excluding irradiation with ultra-violet light. 2-Bromopropaldehyde diethylacetal was obtained as a slightly pink liquid, b. p. 63—64°/14 mm. (yield 63—64%); Stoermer gives b. p. 74—75°/15—16 mm. The bromo-acetal (70 g.) was heated to 125—130° with a solution of ammonia (134 g.) in absolute alcohol (500 g.) in an autoclave with stirring for 7½ hours. 2-Aminopropaldehyde diethylacetal was obtained as a colourless oil, b. p. 64—67° (mainly at 66°)/21 mm. (yield 39%); Burtles, Pyman, and Roylance (*loc. cit.*) give b. p. 79—80°/40 mm. A solution of 2-aminopropaldehyde diethylacetal (7·35 g.) and *N*-methylmorpholine (5·1 g.) in dry chloroform (50 c.c.)

was treated at 0° with one of 2-bromopropionyl bromide (10·8 g.) in dry chloroform (50 c.c.) added dropwise with stirring over 30 minutes. Stirring was continued for one hour during which the mixture was allowed to attain room temperature. The mixture was washed with water, dried, and the solvent removed under reduced pressure. After stripping at 100°/20 mm., the residual yellow oil (11·0 g.) crystallised on standing. Recrystallisation from light petroleum (b. p. 40—60°) at 0° gave 2-(*2-bromopropionamido*)*propaldehyde diethylacetal* as needles, m. p. 56·5—57° (Found: C, 43·0; H, 7·3; N, 4·6. $C_{10}H_{20}O_3NBr$ requires C, 42·6; H, 7·1; N, 4·9%).

2-*Aminopropaldehyde Diethylmercaptal*.—A solution of 2-aminopropaldehyde diethylacetal (18 g.) in water (10 c.c.) was treated successively with concentrated hydrochloric acid (80 c.c.) and ethylthiol (30 c.c.) at 0° and with stirring. The mixture was kept at room temperature for 24 hours with occasional shaking and was then homogeneous. The solution was poured on a mixture of sodium hydroxide solution (40%; 200 c.c.) and cracked ice (500 g.), and the oil which separated was extracted with chloroform (2 × 100 c.c.). The solvent was removed from the dried (sodium sulphate) extract and the residue distilled under reduced pressure to give 2-*aminopropaldehyde diethylmercaptal* as a colourless oil, b. p. 105°/3 mm. (yield, 73%) (Found: C, 46·3; H, 9·3. $C_7H_{17}NS_2$ requires C, 46·9; H, 9·5%). The mercaptal was characterised by the preparation of its *picrate*, which separated from benzene as plates, m. p. 153—154° (Found: C, 38·4; H, 5·2; N, 13·4. $C_{13}H_{20}O_7N_4S_2$ requires C, 38·2; H, 4·9; N, 13·7%).

2-(2-*Bromopropionamido*)*propaldehyde Diethylmercaptal*.—A mixture of 2-aminopropaldehyde diethylmercaptal (19·5 g.), *n*-butylpiperidine (15 g.), and dry chloroform (50 c.c.) was treated with a solution of 2-bromopropionyl bromide (25 g.) in chloroform (50 c.c.) added slowly with stirring at 0°. Stirring was continued for 1 hour at room temperature, and the solution washed successively with water, dilute hydrochloric acid, sodium carbonate solution, and water. After drying, the solvent was removed at 40° under reduced pressure. The residue (31 g.) solidified on standing; it was pressed on a porous tile and crystallised from light petroleum (b. p. 40—60°) to give 2-(*2-bromopropionamido*)*propaldehyde diethylmercaptal* as needles, m. p. 47—48°, which slowly decomposed on standing in air at room temperature (Found: C, 38·2; H, 6·4; N, 4·4. $C_{10}H_{20}ONBrS_2$ requires C, 38·2; H, 6·4; N, 4·5%).

2-*Hydroxy*-3 : 6-*dimethylpyrazine*.—(*a*) Cadmium carbonate (10 g.) was suspended in a solution of 2-(2-bromopropionamido)propaldehyde diethylmercaptal (3·14 g.) in ethanol (50 c.c.) and water (10 c.c.), and the mixture treated with a solution of mercuric chloride (5·6 g.) in ethanol (50 c.c.). The mixture was vigorously stirred for 24 hours, filtered, and the filtrate saturated with ammonia at 0°. After standing at room temperature for 48 hours, the mixture was again filtered, the filtrate evaporated to dryness under reduced pressure, and the residue extracted with warm benzene (100 c.c.). Evaporation of the extract gave a white crystalline solid contaminated with a yellow gum from which it was freed with difficulty and with considerable loss by crystallisation from benzene–light petroleum (b. p. 40—60°). 2-Hydroxy-3 : 6-dimethylpyrazine (250 mg.) was obtained as needles, m. p. 210—211° either alone or when mixed with a specimen prepared by the method described below. For analysis it was sublimed at 120°/10^{-3} mm. without altering the m. p. (Found: C, 58·1; H, 6·8; N, 22·5. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45; N, 22·6%). 2-*Hydroxy*-3 : 6-*dimethylpyrazine picrate* separated from methanol as blades, m. p. 181—185° (Found: N, 19·6. $C_{12}H_{11}O_8N_5$ requires N, 19·8%).

(*b*) 2-Amino-3 : 6-dimethylpyrazine, m. p. 110—112°, was obtained in 20% yield from 2 : 5-dimethylpyrazine (Gabriel and Pinkus, *Ber.*, 1893, **26**, 2197) by the method described by Joiner and Spoerri (*J. Amer. Chem. Soc.*, 1941, **63**, 1929). A solution of this aminopyrazine (0·5 g.) in N-hydrochloric acid (15 c.c.) was treated with sodium nitrite (0·6 g.) added in small portions over 5 minutes at 0° with constant shaking. The solution was kept at room temperature for 2 hours, heated at 60° for 5 minutes, cooled, and neutralised by addition of sodium bicarbonate. The solution was evaporated to dryness under reduced pressure, and the dried residue extracted with boiling benzene (3 × 40 c.c.). Evaporation of the benzene extract gave 2-hydroxy-3 : 6-dimethylpyrazine, which separated from benzene as small felted needles, m. p. 210—211° (yield, 61%). It is very soluble in water and alcohols and sparingly soluble in boiling light petroleum (b. p. 40—60°) (Found: C, 57·9; H, 6·5; N, 22·3. Calc. for $C_6H_8ON_2$: C, 58·1; H, 6·45; N, 22·6%). The picrate separated from methanol as plates, m. p. 181—185°, either alone or when mixed with a specimen prepared by method (*a*).

2-*Hydroxypyrazine*.—The following modification of Gabriel and Sonn's method (*Ber.*, 1907, **40**, 4851) was employed for the preparation of aminopyrazine. Oxidation of quinoxaline gave an 80% yield of pyrazine-2 : 3-dicarboxylic acid which was converted into its dimethyl ester (73% yield) and thence into the diamide (93% yield), which separated as blades from methanol, m. p. 230° (decomp.). Treatment of the diamide with potassium hypobromite solution gave 2-aminopyrazine-3-carboxylic acid (light yellow needles from water, m. p. 210°, decomp.) in 56% yield, and decarboxylation of the amino-acid was effected by refluxing for 10 minutes in nitrobenzene solution to give aminopyrazine as colourless blades, m. p. 117—118° after sublimation at 100°/0·5 mm. (yield 86%). Gabriel and Sonn (*loc. cit.*) give m. p. 110—117°, Hall and Spoerri (*J. Amer. Chem. Soc.*, 1940, **62**, 664), m. p. 117—118°, and Weijlard, Tishler, and Erickson (*ibid.*, 1945, **67**, 804), m. p. 118—120° for aminopyrazine. The last authors obtained 2-aminopyrazine-3-carboxylic acid by hydrolysis of lumazine and effected decarboxylation by boiling the amino-acid with carbityl acetate. Treatment of aminopyrazine with nitrous acid as described in the preparation of 2-hydroxy-3 : 6-dimethylpyrazine (method *b*) gave hydroxypyrazine (yield 30%) as colourless needles from benzene–light petroleum (b. p. 40—60°), m. p. 187—189°. It is soluble in water and ethanol and sparingly soluble in light petroleum and chloroform; it sublimed at 170°/10^{-3} mm. to yield a colourless sublimate, m. p. 187—189° (Found: C, 50·5; H, 4·2. Calc. for $C_4H_4ON_2$: C, 50·0; H, 4·2%). Weijlard, Tishler, and Erickson (*loc. cit.*) describe hydroxypyrazine as forming brilliant yellow needles, m. p. 187—188°. The colour of their product is almost certainly due to impurity; we find that a specimen of the compound prepared as described by them is yellow and that the colour is extremely difficult to remove.

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[*Received, July 2nd*, 1946.]

75. *Pyrazine Derivatives. Part II. A Synthesis of a Racemic 2-Hydroxy-3 : 6-di-sec.-Butylpyrazine and its Relationship to Deoxyaspergillic Acid.*

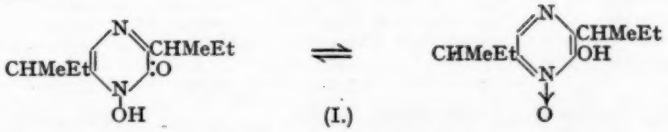
By G. T. Newbold and F. S. Spring.

A synthesis of a racemic *2-hydroxy-3 : 6-di-sec.-butylpyrazine*, m. p. 122—124° (IX), is described using the route adumbrated by (II)—(IX). The synthesis was undertaken as a preliminary step towards the synthesis of the antibacterial compound, aspergillic acid, isolated from culture filtrates of *Aspergillus flavus* by White and Hill. With the object of obtaining the *d*- and *l*-forms corresponding to the racemate, m. p. 122—124°, attempts were made to resolve *2-amino-3 : 6-di-sec.-butylpyrazine* (VIII), the penultimate product of the synthesis. Although the base (VIII) gave a crystalline d-*camphorsulphonate* and a crystalline d-*bromocamphor-π-sulphonate*, fractional crystallisation of these salts did not lead to a resolution. The base (VIII) was also converted into *2-phthalamido-3 : 6-di-sec.-butylpyrazine* (X) which gave a crystalline brucine *salt*; fractionation of this salt likewise failed to effect a resolution.

A comparison of the racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine with deoxyaspergillic acid, $[\alpha]_D$ + 10°, obtained by partial reduction of aspergillic acid by Dutcher and Wintersteiner, is complicated by optical relationships. The ultra-violet absorption spectra of the two compounds are very similar and provide some evidence that deoxyaspergillic acid is a hydroxypyrazine derivative.

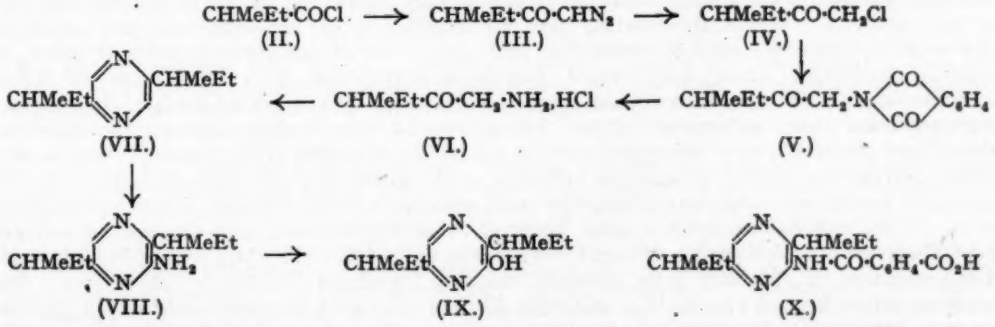
A mould tentatively identified as *Aspergillus flavus* was shown by White (*Science*, 1940, **92**, 127) to grow readily on a medium containing tryptone, yielding filtrates which are bactericidal for some Gram-negative as well as Gram-positive bacteria. White and Hill (*J. Bact.*, 1943, **45**, 433; 1942, **43**, 12) described the isolation of the crystalline antibacterial substance, aspergillic acid, $C_{12}H_{20}O_2N_2$ from the culture filtrates. Glister (*Nature*, 1941, **148**, 470) showed that a mould, probably belonging to the *Aspergillus* genus, produces a powerful antibacterial agent with a range considerably greater than that of penicillin. Menzel, Wintersteiner, and Rake (*J. Bact.*, 1943, **46**, 109) concluded that " the active substance elaborated by Glister's unclassified mould is unquestionably identical with aspergillic acid, m. p. 93°, although the cultural characteristics of this mould are different from those of *Aspergillus flavus* ".

Aspergillic acid was examined by Dutcher and Wintersteiner (*J. Biol. Chem.*, 1944, **155**, 359) who suggest that it is a cyclic hydroxamic acid (I) related to pyrazine. Aspergillic acid can be reduced to a neutral deoxyaspergillic acid for which the structure (IX) was suggested by Dutcher and Wintersteiner.



(I.)

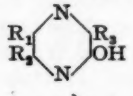
This paper describes a synthesis of a racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (IX) which was undertaken in order to compare this substance with deoxyaspergillic acid and also as a preliminary step in a contemplated synthesis of aspergillic acid. The experience gained in the review of methods for the synthesis of hydroxy-alkylpyrazines described in Part I (preceding paper) led us to choose the following method for the synthesis of the 3 : 6-di-*sec.*-butyl homologue. Methylethylacetyl chloride (II) was converted into *1-chloro-3-methylpentan-2-one* (IV) *via* the diazo-ketone (III). The chloro-ketone was treated in xylene solution with potassium



phthalimide to yield 1-*phthalimido*-3-*methylpentan*-2-*one* (V) which was hydrolysed by means of hydrochloric acid to yield 1-*amino*-3-*methylpentan*-2-*one hydrochloride* (VI). Treatment of the hydrochloride with sodium hydroxide and mercuric chloride gave 2 : 5-di-*sec.*-butylpyrazine (VII) in 11% yield. A very considerable improvement in yield (60%) was achieved by using a modified procedure in which (VI) was treated with sodium hydroxide solution and the reaction product oxidised with hydrogen peroxide; the 2 : 5-di-*sec.*-butylpyrazine was characterised by the preparation of its *chloroplatinate*. Treatment of 2 : 5-di-*sec.*-butylpyrazine in dimethylaniline solution with sodamide gave 2-*amino*-3 : 6-*di*-sec.-*butylpyrazine* (VIII) in high yield. It was characterised by the preparation of a *picrate*, m. p. 134—136°, and several other crystalline derivatives mentioned below. Finally, treatment of the aminopyrazine (VIII) with nitrous acid gave a racemic 2-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine* (IX), m. p. 122—124°, characterised by the formation of its *hydrochloride*.

In order to characterise the synthetic product (IX) the ultra-violet absorption spectra of a number of hydroxypyrazines have been examined. The absorption spectrum of hydroxypyrazine shows a single maximum at 3160 A., whereas 2-hydroxy-3 : 6-dimethylpyrazine and 2-*hydroxy*-3 : 5 : 6-*trimethylpyrazine* show two maxima at approximately 2300 A. and 3300 A. The absorption spectrum of the racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine is very similar, exhibiting maxima at 2285 A. and 3220 A. Dutcher and Wintersteiner (*loc. cit.*) examined the ultra-violet absorption spectrum of deoxyaspergillic acid and observed a single maximum at 3250 A.; they did not observe a band in the neighbourhood of 2300 A. We have re-examined the absorption spectrum of a specimen of deoxyaspergillic acid, m. p. 99—100° (preliminary softening at 96—97°), given to us by Dr. O. Wintersteiner, and find that apart from differences in intensity it is very similar to that of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine, exhibiting maxima at 2295 A., and 3250 A. The differences in intensity may be due to lack of purity in the product from natural sources, since Dr. Wintersteiner informs us (private communication) that specimens of deoxyaspergillic acid have been obtained which melt as high as 105—108°.

Absorption Spectra of Hydroxypyrazines in Ethanol.



R_1.	R_2.	R_3.	λ_{m1} A.	ε_{m1}.	λ_{m2}, A.	ε_{m2}.
H	H	H	—	—	3160	4,200
H	Me	Me	2270	7600	3230	3,600
Me	Me	Me	2295	7900	3360	7,400
H	CHMeEt	CHMeEt	2285	9600	3220	10,000
Deoxyaspergillic acid		(1)	—	—	3250	8,500
"	"	(2)	2295	6700	3250	8,000

(1) Dutcher and Wintersteiner, *loc. cit.* (2) This paper.

A mixture of racemic 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine (m. p. 122—124°) and deoxyaspergillic acid (m. p. 99—100°) melted at 75—85°. In view of the stereochemical complications, this marked depression cannot of course be taken as evidence that deoxyaspergillic acid has not the structure attributed to it by Dutcher and Wintersteiner. Although two racemic forms of 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine are possible, the synthetic material appears to be a single racemate, fractional crystallisation failing to disclose any sign of heterogeneity. Whilst appreciating that the racemate m. p. 122—124° may not belong to the same optical series as deoxyaspergillic acid, $[\alpha]_D$ + 10°, attempts were made to effect its optical resolution. Since 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine is a weak base (it forms a hydrochloride which is decomposed by water) resolution of the parent 2-amino-3 : 6-di-*sec.*-butylpyrazine was attempted. Like 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine, the 2-amino-compound appears to be a single racemate, extensive fractionation of its picrate, and of several other derivatives, failing to disclose evidence of heterogeneity. 2-Amino-3 : 6-di-*sec.*-butylpyrazine would not form crystalline salts with either *d*-tartaric acid or dibenzoyl *d*-tartaric acid. With *d*-camphorsulphonic acid, however, a crystalline salt was obtained, fractional crystallisation of which gave a d-*camphorsulphonate*, m. p. 109—111°, $[\alpha]_D$ + 24°, in high yield. Decomposition of this salt gave optically inactive 2-amino-3 : 6-di-*sec.*-butylpyrazine. The aminopyrazine formed a crystalline salt with *d*-bromocamphor-π-sulphonic acid which likewise gave in high yield a homogeneous d-*bromocamphor-π-sulphonate*, m. p. 167—169°, $[\alpha]_D$ + 55°, the optical rotation remaining constant after repeated crystallisation. Decomposition of the salt gave 2-amino-3 : 6-di-*sec.*-butylpyrazine, $[\alpha]_D$ + 2°. This slight optical rotation is not

significant since the 2-hydroxy-3 : 6-di-*sec*-butylpyrazine obtained by treatment of this specimen of the amine with nitrous acid was optically inactive. The amino-compound obtained by decomposition of the combined mother liquors from the crystallisation of the *d*-bromocamphor-π-sulphonate was also converted into 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine, m. p. 122—124°, which proved to be optically inactive.

In view of this lack of success attending the use of camphor-sulphonic acid salts, it seemed desirable to introduce an acidic function into 2-amino-3 : 6-di-*sec*.-butylpyrazine and to attempt resolution of the resulting acid with a suitable optically active base. Treatment of the amine with succinic anhydride gave 2-*succinimido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 99—101°. This compound proved to be very labile under hydrolytic conditions, treatment with dilute barium hydroxide solution causing quantitative conversion into the parent amine. When treated with aqueous-alcoholic sodium carbonate solution, 2-succinimido-3 : 6-di-*sec*.-butylpyrazine gave 2-*succinamido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 121°, in low yield. The replacement of succinic anhydride by phthalic anhydride proved advantageous, fusion of the amine with the latter giving 2-*phthalimido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 111—112°, in excellent yield; hydrolysis of the latter with dilute alkali yielded 2-*phthalamido*-3 : 6-*di*-sec.-*butylpyrazine*, m. p. 130° (X). The phthalamic rather than the succinamic acid was chosen for resolution experiments because of ease of preparation and greater stability. The phthalamic acid gave a *brucine* salt, m. p. 160—161°, which, after repeated crystallisation, had a slight lævorotation. Decomposition of this salt regenerated the optically inactive phthalamic acid and brucine. Attempts to form a crystalline quinine salt of the phthalamic acid were unsuccessful.

We believe that the close similarity in the ultra-violet absorption spectra of the racemic 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine and deoxyaspergillic acid indicates that the latter is a hydroxypyrazine derivative. A satisfactory explanation for the difficulties encountered in the attempted resolution of 2-amino-3 : 6-di-*sec*.-butylpyrazine and its bearing upon the structure of deoxyaspergillic acid must await further investigation.

Experimental.

1-*Chloro*-3-*methylpentan*-2-*one*.—Methylethylacetic acid (*Org. Synth.*, V, 75) was converted into its acid chloride using the method described by Brown (*J. Amer. Chem. Soc.*, 1938, **60**, 1325; cf. Hudson and Hauser, *ibid.*, 1941, **63**, 3156). The acid chloride, b. p. 117° (yield 70—75%), was characterised by the preparation of methylethylacetamide which separated from ether as small needles, m. p. 111—112°. Methylethylacetyl chloride (40 g.) in dry ether (100 c.c.) was added slowly to a dry solution of diazomethane in ether (700 c.c., prepared from 80 g. of nitrosomethylurea) with shaking and cooling with ice-water. The reaction vessel was fitted with a soda-lime tube and the solution left for 15 hours. The solution was then cooled in ice and treated with a stream of dry hydrogen chloride (2—3 hours). The reaction mixture was left overnight and washed first with saturated sodium carbonate solution until the ether phase was neutral and then with water, and dried (Na_2SO_4). The ether was removed and the light brown oil distilled under reduced pressure to give a main fraction, b. p. 60—70°/15 mm., which on redistillation yielded 1-*chloro*-3-*methylpentan*-2-*one* as a colourless oil, b. p. 62—64°/14 mm., $n_D^{17°}$ 1·4385 (yield, 69—79%). The chloro-ketone has a penetrating, but not markedly lachrymatory, odour (Found : C, 54·0; H, 8·3. $C_6H_{11}OCl$ requires C, 53·6; H, 8·2%).

1-*Phthalimido*-3-*methylpentan*-2-*one*.—A mixture of 1-chloro-3-methylpentan-2-one (20 g.), dry xylene (35 c.c.), and potassium phthalimide (30 g.) was heated at 140—150° (bath temp.) with stirring for 4 hours. After cooling, the mixture was diluted with hot benzene and filtered. The filtrate was concentrated under reduced pressure and then treated with light petroleum (b. p. 40—60°). The crystalline solid which separated on cooling (24·5 g., m. p. 80—83°) was collected and recrystallised from light petroleum (b. p. 40—60°) to give 1-*phthalimido*-3-*methylpentan*-2-*one* as long fine needles, m. p. 84—86°, not raised by further recrystallisation (yield, 65%) (Found : C, 68·6; H, 6·3; N, 5·4. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%).

1-*Amino*-3-*methylpentan*-2-*one Hydrochloride*.—The phthalimido-ketone (10·8 g.) was heated under reflux with hydrochloric acid (120 c.c.; 20%) for 24 hours. The solution was allowed to cool, and the separated phthalic acid filtered off and washed with a little ice-water. The filtrate and washings were combined and evaporated to dryness under reduced pressure. Ice-water (50 c.c.) was added and the mixture filtered and again evaporated to dryness. The residue was dissolved in warm methanol (20 c.c.) and diluted with an equal volume of dry ether. The solution was cooled to − 20°; the hydrochloride then separated as shining plates. A further crop was obtained from the mother liquors (yield, 87%). Recrystallisation from methanol–ether with refrigeration gave 1-*amino*-3-*methylpentan*-2-*one hydrochloride* as plates which sintered at 130—140° and were completely molten at 160°, a property not changed by further recrystallisation (Found : Cl, 23·8. $C_6H_{14}ONCl$ requires Cl, 23·4%).

2 : 5-*Di*-sec.-*butylpyrazine*.—(*a*) A solution of the amino-ketone hydrochloride (6 g.) in ice-water (25 c.c.) was cooled (ice-water) and treated with sodium hydroxide solution (50 c.c.; 33%). The oil which separated was isolated by means of ether and dissolved in methanol. The solution was cooled to 0°, treated with hydrogen peroxide (5 c.c.; 30%), and set aside for 4 hours. Palladised charcoal (0·5 g. 5%) was added and the mixture set aside overnight. After filtration, the methyl alcohol was removed under reduced pressure, and the residue treated with water and thrice extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated, and the oil was distilled under reduced pressure

to give 2 : 5-di-*sec.*-butylpyrazine as a light yellow oil, b. p. 112—117°/13 mm. (yield, 60%). The *chloroplatinate* separated from methanol as orange-red needles, m. p. 183° (decomp.) [Found : C, 36·3; H, 5·4; Pt, 24·5, 24·8; Cl, 26·3. $(C_{12}H_{20}N_2)_2,H_2PtCl_6$ requires C, 36·3; H, 5·3; Pt, 24·6; Cl, 26·8%].

(*b*) A solution of 1-amino-3-methylpentan-2-one hydrochloride (15·2 g.) in water (15 c.c.) was treated with sodium hydroxide solution (250 c.c.; 33%) with ice-cooling. Finely powdered mercuric chloride (40 g.) was added and the mixture steam distilled. The distillate (500 c.c.) was treated with mercuric chloride solution and the mercurichloride which separated was collected. The mercurichloride was distilled with potassium hydroxide solution (50%; 30 c.c.) and the oily distillate collected, dried (KOH), and distilled to give 2 : 5-di-*sec.*-butylpyrazine as a light yellow coloured oil, b. p. 113°/11 mm. (yield, 11%). Its chloroplatinate separated from methanol as orange-red needles, m. p. 183° (decomp.) not depressed when mixed with the specimen described under (*a*).

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine*.—A solution of 2 : 5-di-*sec.*-butylpyrazine (4·2 g.) in freshly distilled dimethylaniline (10 c.c.) was added to finely powdered, freshly prepared sodamide (4·0 g.). The mixture was heated at 165° (bath temp.) for 2 hours with vigorous mechanical stirring. The mixture was cooled and poured on crushed ice. The aqueous phase was saturated with potassium carbonate and the mixture thrice extracted with ether. The ethereal extract was dried (Na_2SO_4) and the ether removed. Dimethylaniline was removed at 15 mm. and the remaining oil distilled to give the aminopyrazine, b. p. 110—120°/1 mm. (yield, 60—65%). Purification was achieved by conversion into the *picrate* which separated from methanol or ethanol as yellow needles, m. p. 134—136° (Found : C, 49·6; H, 5·6; N, 19·7. $C_{18}H_{24}O_7N_6$ requires C, 49·5; H, 5·5; N, 19·3%). Decomposition of the picrate by treatment with lithium hydroxide solution (cf. Burger, *J. Amer. Chem. Soc.*, 1945, **67**, 1615) and isolation of the product by means of ether followed by distillation gave 2-*amino*-3 : 6-di*sec.*-*butylpyrazine* as a colourless oil, b. p. 112—114°/0·5 mm. (97% yield) (Found : C, 69·3; H, 10·1; N, 20·1. $C_{12}H_{21}N_3$ requires C, 69·6; H, 10·1; N, 20·3%). A sample of the once-distilled base (3·7 g., b. p. 110—120°/1 mm.) was treated with successive portions of ethanolic picric acid, each containing approximately 0·5 g. of picric acid to give seven crops of picrate each of which melted within the range 131—136°. Each crop gave no depression in m. p. when mixed with the preceding one; the total picrate recovered (6·75 g.) represents 85% of the initial base.

2-*Hydroxy*-3 : 6-*di*-sec.-*butylpyrazine*.—A solution of 2-amino-3 : 6-di-*sec.*-butylpyrazine (2·1 g.) in N-hydrochloric acid (50 c.c.) was treated with sodium nitrite (2·0 g.) added in small portions with shaking, the mixture being cooled in ice-water. The mixture was kept at room temperature for 2—3 hours, warmed to 50—60° for five minutes, cooled, and neutralised by addition of sodium bicarbonate. The mixture was extracted with ether and the extract repeatedly washed with N-sodium hydroxide solution. The alkaline extract was acidified to litmus with dilute hydrochloric acid. After cooling to 0°, the solid was collected (1·55 g.), washed with water, and crystallised from aqueous methanol from which 2-*hydroxy*-3 : 6-*di*-sec.-*butylpyrazine* separated as prismatic needles (or as prisms from concentrated solutions), m. p. 122—123°. 2-Hydroxy-3 : 6-di-*sec.*-butylpyrazine sublimes rapidly at 120°/0·005 mm. It is readily soluble in cold ether, light petroleum, benzene, chloroform and acetone, insoluble in cold water, slightly soluble in hot water, and readily soluble in cold 3N-sodium hydroxide and 3N-hydrochloric acid. In admixture with an equal quantity of deoxyaspergillic acid (m. p. 99—100°) it melted at 75—85° (Found : C, 69·0; H, 9·4; N, 13·5. $C_{12}H_{20}ON_2$ requires C, 69·2; H, 9·6; N, 13·5%).

The *hydrochloride* was obtained by treating a dry ethereal solution of the hydroxy-pyrazine with dry hydrogen chloride; it separates from ethanol–ether as small prismatic needles, m. p. 173—175°. (Found : C, 59·6; H, 8·6; N, 11·1. $C_{12}H_{21}ON_2Cl$ requires C, 58·9; H, 8·6; N, 11·45%). When a solution of the hydrochloride in ethanol is diluted with water, 2-hydroxy-3 : 6-di-*sec.*-butylpyrazine separates, m. p. 122—123°.

2-(2-*Bromopropionamido*)butan-3-*one*.—A solution of 2-aminobutan-3-one hydrochloride (Fargher and Pyman, *J.*, 1919, 233) (18·2 g.) in water (80 c.c.) was added rapidly to a well stirred ice-cooled suspension of powdered calcium carbonate (50 g.) in dry chloroform (150 c.c.). To this mixture was added a solution of 2-bromopropionyl bromide (50 g.) in dry chloroform (100 c.c.). After being stirred for 5 minutes the mixture was filtered and the chloroform layer separated, washed with water, and evaporated under reduced pressure. The residue crystallised on trituration with light petroleum; after four recrystallisations from benzene–light petroleum 2-(2-*bromopropionamido*)*butan*-3-*one* was obtained as prismatic needles, m. p. 77—79° (Found : C, 38·1; H, 5·3. $C_7H_{12}O_2NBr$ requires C, 37·9; H, 5·4%).

2-*Hydroxy*-3 : 5 : 6-*trimethylpyrazine*.—A solution of 2-(2-bromopropionamido)butan-3-one (5·0 g.) in dry ethanol (30 c.c.) containing sodium iodide (0·5 g.) was saturated with dry ammonia at 0° and kept at room temperature for 48 hours. The solvent was removed under reduced pressure and the gummy residue extracted with hot benzene. Concentration of the benzene extract gave a crop of red needles (1·0 g.), m. p. 196—198°, which was purified by sublimation at 120°/0·01 mm.; the *pyrazine* was thus obtained as colourless needles, m. p. 197—199° (Found: C, 60·9; H, 7·1; N, 20·1. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·2; N, 20·3%).

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*Camphor*-β-*sulphonate*.—A mixture of 2-amino-3 : 6-di-*sec.*-butylpyrazine (0·877 g.) and *d*-camphor-β-sulphonic acid (0·992 g.) was dissolved in a warm mixture of water (10 c.c.) and methanol (2 c.c.). Since the salt did not separate on cooling, the solvent was removed under reduced pressure and the residual gum dissolved in ethyl acetate (1 c.c.) and ether (15 c.c.). The solution was repeatedly agitated; after three days crystal formation was observed, and on agitation a massive crystalline deposit rapidly separated. The prismatic crystals (1·15 g.), m. p. 104—108°, were collected (crop *A*) and the mother liquor concentrated to give a second crop of prisms, m. p. 101—105° (0·5 g.) (crop *B*). Crops *A* and *B* together represent 85% of the theoretical yield of salt. Crop *A* (0·5 g.) was thrice recrystallised from ether–light petroleum (b. p. 40—60°) to yield 2-*amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*camphor*-β-*sulphonate* (0·25 g.) as prisms, m. p. 109—111°, $[\alpha]_D^{21°}$ + 24° (*l*, 1; *c*, 2·1 in chloroform), not altered by further recrystallisation (Found : C, 60·4; H, 8·6; N, 9·6. $C_{22}H_{37}O_4N_3S$ requires C, 60·1; H, 8·4; N, 9·6%). Crop *B* was thrice crystallised from ether–light petroleum (b. p.

40—60°) to yield 0·3 g. of the same salt, m. p. 108—111°, $[\alpha]_D^{20°}$ + 22·5° (*l*, 1; *c*, 2·6 in chloroform). Concentration of the mother liquors from crops *A* and *B* followed by recrystallisation, gave a further quantity (0·35 g.) of the same salt, m. p. 108—111°, $[\alpha]_D^{20°}$ + 23° (*l*, 1; *c*, 3·0 in chloroform). Decomposition of the salt, $[\alpha]_D$ + 23°, by shaking with sodium hydroxide solution (10%) followed by chloroform extraction gave the parent amino-pyrazine, $[\alpha]_D^{16°}$ ± 0° (*l*, 1; *c*, 3·0 in chloroform); it was characterised by its picrate, m. p. 134—136°.

2-*Amino*-3 : 6-*di*-sec.-*butylpyrazine* d-*Bromocamphor-π-sulphonate*.—A solution of ammonium *d*-bromocamphor-π-sulphonate {m. p. 278° decomp., $[\alpha]_D^{18°}$ + 85° (*l*, 1; *c*, 3·8 in water) $[\alpha]_D^{18·5°}$ + 94° (*l*, 1; *c*, 3·1 in methanol)} (1·0 g.) in water (10 c.c.) was boiled with 0·5N-barium hydroxide solution (10 c.c.) until ammonia evolution ceased. The solution was cooled and exactly neutralised with 0·5N-sulphuric acid, and the barium sulphate was removed. The filtrate was evaporated at 30° under reduced pressure to a viscous syrup, which was dried over phosphoric oxide in a vacuum. A solution of 2-amino-3 : 6-di-*sec*.-butylpyrazine (0·63 g.) in chloroform (20 c.c.) was added to the syrupy sulphonic acid. Crystallisation of the salt did not occur using either chloroform or ethyl acetate as solvent but was achieved from ether–light petroleum (b. p. 40—60°) from which a crop of heavy prisms separated, m. p. 156—161°, $[\alpha]_D^{18°}$ + 55° (*l*, 1; *c*, 3·0 in chloroform) (1·2 g. or 82%), which on crystallisation attained the constant m. p. 167—169°, $[\alpha]_D^{18°}$ + 55° (*l*, 1; *c*, 2·5 in chloroform), not altered by further recrystallisations (Found: C, 51·6; H, 7·0; N, 7·8. $C_{22}H_{36}O_4N_2BrS$ requires C, 51·1; H, 7·0; N, 8·1%). The base (0·15 g.) regenerated from a specimen of salt (0·57 g.), m. p. 164—167°, $[\alpha]_D^{18°}$ + 55°, had $[\alpha]_D^{18°}$ + 2° (*l*, 0·5; *c*, 3·0), a value within the limits of experimental error. This specimen of the base was treated with nitrous acid to give 2-hydroxy-3 : 6-di-*sec*.-butylpyrazine (0·1 g.), m. p. 121—122°, $[\alpha]_D^{18°}$ ± 0° (*l*, 0·5; *c*, 5·5 in ethanol). Similarly, the base regenerated from the combined mother liquors of the twice recrystallised salt was converted into the hydroxy-pyrazine (0·15 g.), m. p. 118—120°, $[\alpha]_D^{20°}$ ± 0° (*l*, 0·5; *c*, 3·0 in ethanol), which after a single recrystallisation from aqueous ethanol had m. p. 121—122°.

2-*Succinimido*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of succinic anhydride (0·55 g.) and 2-amino-3 : 6-di-*sec*.-butylpyrazine (1·1 g.) was heated at 120—125° for 45 minutes. After cooling, the reaction mixture was dissolved in chloroform and the solution washed with 3N-sodium hydroxide, then with water, and dried (Na_2SO_4). The chloroform was removed, the resulting gum crystallising on cooling; recrystallisation from *n*-hexane gave 2-*succinimido*-3 : 6-*di*-sec.-*butylpyrazine* as prisms, m. p. 99—101° (yield, 62%). It is readily soluble in the common organic solvents with the exception of light petroleum, and is insoluble in water, 3N-sodium hydroxide, and 3N-hydrochloric acid (Found: C, 66·6; H, 8·0; N, 14·2. $C_{16}H_{23}O_2N_3$ requires C, 66·4; H, 8·0; N, 14·5%).

The succinimido-derivative (0·3 g.) in ethanol (5 c.c.) was treated with 0·5N-barium hydroxide (15 c.c.) and refluxed for 30 minutes. The ethanol was removed by distillation and the oil which separated was isolated by means of chloroform. Distillation at 100°/15 mm. gave 2-amino-3 : 6-di-*sec*.-butylpyrazine (0·19 g.) characterised as its picrate which separated from ethanol as needles, m. p. 133—135° not depressed when mixed with the authentic specimen of m. p. 134—136°.

2-*Succinamido*-3 : 6-*di*-sec.-*butylpyrazine* [N-(3 : 6-*Di*-sec.-*butyl*-2-*pyrazyl*)*succinamic Acid*].—A solution of the succinimido-derivative (0·25 g.) in methanol (2 c.c.) and sodium carbonate solution (10%; 3 c.c.) was heated under reflux for 1 hour. The mixture was diluted with an equal volume of water and extracted with ether. Evaporation of the ether gave a viscous oil which on treatment with ethanolic picric acid gave the picrate of 2-amino-3 : 6-di-*sec*.-butylpyrazine, m. p. and mixed m. p. 133—135° (0·13 g.). The aqueous phase was acidified to Congo-red with hydrochloric acid and the solution evaporated at 30° under reduced pressure to a small bulk. The resinous solid separating was dissolved in cold N-sodium hydroxide solution and the solution again acidified to Congo-red. Careful evaporation of the solution gave a crystalline solid (0·14 g.), m. p. 119—121°. Crystallisation of this from aqueous methanol gave 2-*succinamido*-3 : 6-*di*-sec.-*butylpyrazine* as prisms, m. p. 121—122° (Found: equiv., 312. $C_{16}H_{25}O_3N_3$ requires equiv., 307).

2-*Phthalimido*-3 : 6-*di*-sec.-*butylpyrazine*.—A mixture of 2-amino-3 : 6-di-*sec*.-butylpyrazine (1·0 g.) and phthalic anhydride (0·8 g.) was slowly heated to 180° (bath temp.) and maintained at 170—180° for 5 minutes. The cold reaction product was dissolved in chloroform, and the solution washed successively with N-sodium hydroxide solution and water, and dried. The solvent was removed, and crystallisation induced by the addition of light petroleum and cooling. Recrystallisation from light petroleum (b. p. 40—60°) gave 2-*phthalimido*-3 : 6-*di*-sec.-*butylpyrazine* as rosettes of prismatic needles, m. p. 111—112° (yield, 83%) (Found: C, 71·2; H, 6·8; N, 12·1. $C_{20}H_{23}O_2N_3$ requires C, 71·2; H, 6·8; N, 12·5%).

2-*Phthalamido*-3 : 6-*di*-sec.-*butylpyrazine* [N-(3 : 6-*Di*-sec.-*butyl*-2-*pyrazyl*)*phthalamic Acid*].—A solution of the phthalimido-derivative (1·35 g.) in ethanol (15 c.c.) and potassium hydroxide solution (5%; 15 c.c.) was heated under reflux for 1½ hours. The ethanol was removed by distillation, and the solution diluted with an equal volume of water and acidified to Congo-red with dilute hydrochloric acid. The precipitated acid was collected (1·3 g., m. p. 128—129°) and crystallised from aqueous alcohol from which 2-*phthalamido*-3 : 6-*di*-sec.-*butylpyrazine* separated as small needles, m. p. 130° (Found: equiv., 350. $C_{20}H_{25}O_3N_3$ requires equiv., 355). The phthalamic acid was readily hydrolysed to 2-amino-3 : 6-di-*sec*.-butylpyrazine by refluxing for 30 minutes with 5N-hydrochloric acid; the base was c haracterised as its picrate which separated as yellow needles from ethanol, m. p. 134—136°.

A solution of the phthalamic acid (0·75 g.) and brucine {0·85 g.; m. p. 174—176°, $[\alpha]_D^{18°}$ − 109° (*l*, 1; *c*, 2·45 in chloroform)} in acetone (25 c.c.) containing a little ether was set aside for several hours; the separated brucine salt was then collected (m. p. 158—159°; 1·4 g., 90%). Fractional crystallisation from chloroform–ethyl acetate gave a constant-melting *salt*, m. p. 160—161° (0·45 g.), $[\alpha]_D^{20°}$ − 10° (*l*, 0·5; *c*, 4·2 in chloroform) (Found: N, 9·3. $C_{43}H_{51}O_7N_5$ requires N, 9·35%). Decomposition of the salt (0·15 g.) by dilute hydrochloric acid gave the phthalamic acid (50 mg.), m. p. 129—130°, $[\alpha]_D^{20°}$ ± 0° (*l*, 1; *c*, 12·9 in alcohol).

We wish to express our sincere thanks to Dr. O. Wintersteiner and Dr. J. D. Dutcher of the Squibb Institute for Medical Research, New Jersey, for their kindness in supplying us with a specimen of

deoxyaspergillic acid and for placing at our disposal various unpublished data concerning this compound, to Dr. A. E. Gillam, who determined the ultra-violet absorption spectra, and to Dr. T. H. H. Quibell for gifts of *d*-camphor-β-sulphonic acid and ammonium *d*-bromocamphor-π-sulphonate.

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[*Received, July 2nd*, 1946.]

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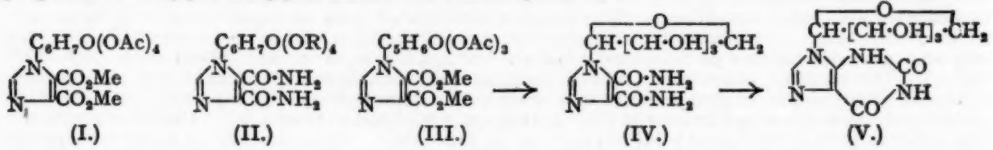
76. *Application of the Hofmann Reaction to the Synthesis of Heterocyclic Compounds. Part IV. The Synthesis of* 9-d-*Xylopyranosidoxanthine.*

By R. A. BAXTER and F. S. SPRING.

Treatment of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-*d* xylose gives *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* (III) which on treatment with alcoholic ammonia yields 1-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* (IV). Treatment of the latter with alkaline potassium hypobromite solution gives 9-d-*xylopyranosidoxanthine* (V) in good yield.

WHEN the work described in this series of papers was first envisaged, one of the principal objectives was to attempt to apply the intramolecular Hofmann reaction to a suitably substituted glyoxaline dicarboxyamide to effect a synthesis of a purine glycoside of the xanthosine (9-*d*-ribofuranosidoxanthine) type. It was appreciated that at least three major hurdles would have to be negotiated before this could be achieved. First, such a synthesis would require that a 1-substituted glyoxaline-4 : 5-dicarboxyamide should give mainly a 9-substituted xanthine rather than the 7-substituted isomer. Secondly, it would require the development of a method for the introduction of a suitable glycosidic group at position 1 in glyoxaline-4 : 5-dicarboxyamide and, thirdly, it required the establishment of conditions for the intramolecular ring closure of this glycoside. In Part II (Baxter and Spring, *J.*, 1945, 232) we described the synthesis in high yield of 9-methylxanthine from 1-methylglyoxaline-4 : 5-dicarboxyamide, a reaction which encouraged us to believe that the first hurdle had been successfully negotiated and led us to turn our attention to a study of the preparation and properties of 1-glycosidoglyoxaline-4 : 5-dicarboxyamides.

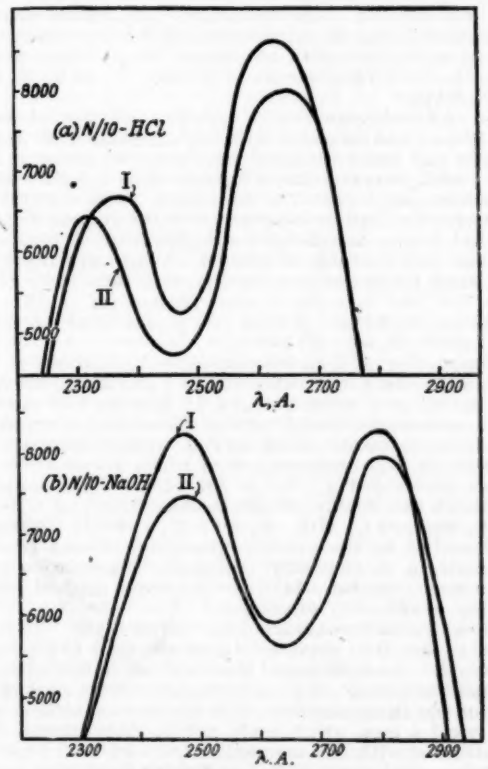


(I.) (II.) (III.) (IV.) (V.)

Treatment of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate (Baxter and Spring, *loc. cit.*) with acetobromo-*d*-glucose gave *methyl* 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate* (I). The reaction proceeds smoothly to give excellent yields if the silver salt is obtained in a granular form and special precautions are observed to ensure purity of materials (cf. Gulland and Macrae, *J.*, 1933, 662). When the glucoside (I) is treated with methanolic ammonia, simultaneous deacetylation and amidation occur to give 1-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* (II, R = H) which, when treated with acetic anhydride and pyridine, yields 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* (II, R = Ac). Condensation of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with the appropriate acetobromo-sugar followed by treatment of the product with methanolic ammonia gave 1-l- and 1-d-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*; acetylation of the 1-*l*-isomer yielded 1-*triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*. Acetylation of the 1-*d*-isomer gave an oil which could not be crystallised. Condensation of the silver salt of methyl glyoxaline-4 : 5-dicarboxylate with acetobromo-*d*-xylose gave *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* (III) which with alcoholic ammonia yielded 1-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* (IV). Acetylation of the latter compound gave 1-*triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.

Treatment of 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (II, R = H) with alkaline potassium hypobromite under the conditions employed in the preparation of 9-methylxanthine *loc. cit.*) gave a glycosidic product which was isolated by precipitation as a barium salt; the extremely low yield, however, did not allow further purification or characterisation. Many variations in reaction conditions were made, including the use of barium hypobromite with the

object of achieving rapid separation of the barium salt of the purine glycoside from the reaction mixture; all these attempts were unsuccessful. 1-Tetra-acetyl-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (II, R = Ac) was recovered unchanged after treatment with alkaline potassium hypobromite solution. Treatment of 1-*l*-arabinosidoglyoxaline-4 : 5-dicarboxyamide with alkaline potassium hypobromite gave a very small yield of a product which appeared to be a 9-glycosidoxanthine since it gave a positive Molisch reaction and its ultra-violet absorption spectrum was very similar to that of 9-methylxanthine. The low yield, however, precluded a successful purification and, as in the previous case, variations in reaction conditions did not lead to an improvement in yield. A similar behaviour was observed in the case of 1-*d*-arabinosidoglyoxaline-4 : 5-dicarboxyamide. 1-Triacetyl-*l*-arabinosidoglyoxaline-4 : 5-dicarboxyamide, which is very insoluble in water, was recovered unchanged after treatment with alkaline potassium hypobromite.



I. 9-*Methylxanthine.*
II. 9-d-*Xylopyranosidoxanthine.*

Treatment of 1-*d*-xylopyranosidoglyoxaline-4 : 5-dicarboxyamide with alkaline potassium hypobromite gave 9-d-*xylopyranosidoxanthine* (V) in good yield. The glycoside (V) crystallises from water in well-formed microscopic needles which slowly decompose on heating above 250°. Hydrolysis of 9-*d*-xylopyranosidoxanthine with dilute sulphuric acid gives a mixture of *d*-xylose (characterised as its tetra-acetyl derivative) and xanthine. The latter was characterised by the preparation of its perchlorate and by its ultra-violet absorption spectrum. The ultra-violet absorption spectra of 9-*d*-xylopyranosidoxanthine in both acid and alkali (see fig.) are virtually identical with those of 9-methylxanthine (see fig.) and with those of xanthosine (Gulland, Holiday, and Macrae, *J.*, 1934, 1643) and show that the synthetic material is a 9- and not a 7-glycosidoxanthine.

Oxidation of the synthetic 9-xylosidoxanthine and of the parent 1-*d*-xylosidoglyoxaline-4 : 5-dicarboxyamide with periodate (Lythgoe and Todd, *J.*, 1944, 592) shows that the glycosidic residue in both compounds is of the pyranose form. We believe that the glycoside residues in all the 1-glycosidoglyoxaline-4 : 5-dicarboxyamides described in this paper are of the pyranose form although this has only been rigorously established in the case of the *d*-xyloside.

The behaviour of 9-*d*-xylopyranosidoxanthine, xanthosine, and 9-methylxanthine when treated with acetic anhydride will form the subject of a later communication.

Experimental.

Methyl 1-*Tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate*.—A solution of methyl glyoxaline-4 : 5-dicarboxylate (Baxter and Spring, *loc. cit.*) (6·1 g.) in aqueous methanol (50%; 300 c.c.) was treated at 50° with one of silver nitrate (5·7 g.) in water (50 c.c.), added rapidly with stirring. The mixture was made just alkaline by the addition of dilute aqueous ammonia (10 c.c., of *d* 0·88 in 90 c.c. of water) and kept at 55—60°, the precipitated silver salt then becoming granular. The mixture was cooled in the dark, the silver salt collected, washed successively with water, methanol, and ether, and dried in a vacuum in the dark (yield 9·4 g.). The silver salt was suspended in sulphur-free xylene (350 c.c.), and the suspension finally dried in the usual manner by removal of solvent (approx. 50 c.c.) through a Fenské-type column. To the resulting suspension was added freshly prepared acetobromo-*d*-glucose (12·5 g.), and the mixture refluxed in an oil-bath at 180° until the solution no longer gave a positive halogen test (approx. 15 mins.). The mixture was filtered, cooled to 45°, and filtered again to remove a small quantity of methyl glyoxaline-4 : 5-dicarboxylate. The filtrate was evaporated under reduced pressure, and the residual gum dissolved in hot methanol (150 c.c.). On cooling *methyl* 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxylate* separated as prisms (10 g.) which after a recrystallisation had m. p. 123°, $[\alpha]_D^{19°}$ + 16° (*l* = 1, *c* = 2·5 in chloroform) (Found: C, 48·6; H, 4·8; N, 5·4. $C_{21}H_{26}O_{13}N_2$ requires C, 49·0; H, 5·1; N, 5·4%).

1-d-*Glucosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of the above tetra-acetyl derivative (6·5 g.) in dry methanol (150 c.c.) was saturated with dry ammonia at 0° and kept at this temperature for 48 hours. The ammonia and some methanol were removed under reduced pressure, the amide (4·5 g.) rapidly separating. After recrystallisation from pyridine 1-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as small needles, m. p. 232—233° (decomp.). This diamide (2·5 g.) was also prepared by similar treatment of the gum obtained by evaporation of the original methanolic mother-liquor from the crystallisation of methyl 1-tetra-acetyl-*d*-glucosidoglyoxaline-4 : 5-dicarboxylate. The amide is slightly soluble (1%) in water and insoluble in ethanol. When crystallised from aqueous ethanol, it separates as a *monohydrate* which forms feathery needles, m. p. 146—148°. The water of crystallisation was not lost on drying at 135°/10^{-2} mm. for 6 hours [Found (m. p. 232—233°): C, 42·0; H, 5·2. $C_{11}H_{16}O_7N_4$ requires C, 41·8; H, 5·1%. Found (m. p. 146—148°): C, 39·2; H, 5·1; N, 16·3. $C_{11}H_{16}O_7N_4,H_2O$ requires C, 39·5; H, 5·4; N, 16·8%].

1-*Tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide*.—A solution of anhydrous 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide (4·5 g.) in pyridine (25 c.c.) and acetic anhydride (25 c.c.) was kept at 0° for 24 hours, and then heated on a water-bath for 10 minutes and carefully diluted with ethanol (50 c.c.). The mixture was concentrated under reduced pressure until crystallisation commenced; the acetyl derivative separated from this mixed solvent as long needles containing pyridine of crystallisation which was lost on crystallisation from methanol, from which 1-*tetra-acetyl*-d-*glucosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as prisms (5·1 g.), m. p. 162—163°. This diamide is insoluble in water, moderately soluble in methanol, and readily soluble in chloroform and benzene (Found: C, 46·8; H, 5·3; N, 11·3. $C_{19}H_{24}O_{11}N_4$ requires C, 47·1; H, 5·1; N, 11·6%). When treated with methanolic ammonia by the method described in the previous paragraph, it was converted into 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide, m. p. 232—233° (decomp.). Acetylation of hydrated 1-*d*-glucosidoglyoxaline-4 : 5-dicarboxyamide, m. p. 146—148°, by the same method, also gave this tetra-acetyl derivative, m. p. and mixed m. p. 162—163° (decomp.).

1-l-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*.—The silver salt of methyl glyoxaline-4 : 5-dicarboxylate was prepared as described previously from the ester (9·2 g.) and silver nitrate (8·5 g.), and dried by the xylene method. A suspension of the silver salt in boiling xylene (400 c.c.) was treated with a solution of acetobromo-*l*-arabinose (13 g.) in hot xylene (100 c.c.), and the mixture heated under reflux for 10 minutes; reaction was then complete. The mixture was filtered, and the filtrate evaporated under reduced pressure to yield a gum which could not be crystallised. A solution of this gum in methanol (200 c.c.) was saturated with dry ammonia at 0° and then kept at 0° for 24 hours. The crystalline mass which had separated was collected and crystallised from aqueous alcohol, from which 1-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as needles (8·2 g.) sintering at 175—180° and melting at 215—216° (decomp.); $[\alpha]_D^{22°}$ + 44° (*l* = 1, *c* = 1·5 in pyridine) (Found: C, 40·8; H, 5·3; N, 18·5. $C_{10}H_{14}O_6N_4,\frac{1}{2}H_2O$ requires C, 40·7; H, 5·1; N, 19·0%).

1-*Triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide*.—1-l-Arabinosidoglyoxaline-4 : 5-dicarboxyamide was acetylated at 0° by treatment with pyridine (5 c.c.) and acetic anhydride (5 c.c.). The product was crystallised first from ethanol and then from ether–light petroleum (b. p. 40—60°) to give 1-*triacetyl*-l-*arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* as plates, m. p. 132—133° (Found: C, 46·6; H, 5·0. $C_{16}H_{20}O_9N_4$ requires C, 46·6; H, 4·9%).

1-d-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide* was obtained from acetobromo-*d*-arabinose and the silver salt of methyl glyoxaline-4 : 5-dicarboxylate by the method described for the *l*-isomer. It separated from aqueous ethanol as needles, m. p. 216° (sintering at 175—180°), $[\alpha]_D^{19°}$ − 40° (*l* = 1, *c* = 1·7 in pyridine). As in the case of the *l*-isomer it separates with water of crystallisation which is very tenaciously held (Found: C, 41·0; H, 5·0; N, 18·9. $C_{10}H_{14}O_6N_4,\frac{1}{2}H_2O$ requires C, 40·7; H, 5·1; N, 19·0%).

Methyl 1-*Triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate*.—Condensation of the dry silver salt of methyl glyoxaline-4 : 5-dicarboxylate (from 11 g. of ester) with acetobromo-*d*-xylose (16·5 g.) in sulphur-free, dry xylene (600 c.c.) was effected in the manner previously described. After removal of silver bromide, the filtrate was cooled; the product then separated, and recrystallisation from methanol gave *methyl* 1-*triacetyl*-d-*xylosidoglyoxaline*-4 : 5-*dicarboxylate* as needles (10 g.), m. p. 166—167°, $[\alpha]_D^{20°}$ + 22·6° (*l* = 1, *c* = 1·8 in chloroform) Found: C, 49·0; H, 5·1. $C_{18}H_{22}O_{11}N_4$ requires C, 48·9; H, 5·0%).

1-d-*Xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.—Methyl 1-triacetyl-*d*-xylosidoglyoxaline-4 : 5-dicarboxylate (8·5 g.) was dissolved in methanol (200 c.c.) saturated with dry ammonia at 0°. The solution was kept at room temperature for 18 hours. The ammonia was removed under reduced pressure, and the product then crystallised. Recrystallisation from aqueous ethanol gave 1-*d*-xylopyranosidoglyoxaline-4 : 5-dicarboxyamide as needles (4·5 g.) sintering at 165—170° and melting at 224—225° (decomp.), $[\alpha]_D^{19°}$ + 34° (l = 4, c = 0·3 in water). The amide separated as a *monohydrate* and the water of crystallisation was not lost on drying for 8 hours at 135° in a high vacuum over phosphoric oxide (Found: C, 39·9; H, 5·1; N, 18·3. $C_{10}H_{14}O_6N_4.H_2O$ requires C, 39·5; H, 5·3; N, 18·4%). Removal of the solvent from the original xylene mother-liquor of methyl 1-triacetyl-*d*-xylosidoglyoxaline-4 : 5-dicarboxylate gave a gum which on treatment with methanolic ammonia as described above gave a further quantity (5 g.) of this diamide, m. p. 224—225° (sintering at 165—170°).

1-*Triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide*.—1-*d*-Xylopyranosidoglyoxaline-4 : 5-dicarboxyamide (1 g.) was acetylated by treatment with pyridine (5 c.c.) and acetic anhydride (5 c.c.) by the method previously described. After addition of ethanol and removal of the mixed solvent under reduced pressure, the residue was crystallised from ethanol, from which 1-*triacetyl*-d-*xylopyranosidoglyoxaline*-4 : 5-*dicarboxyamide* separated as needles (1·1 g.), m. p. 158—159° (Found: C, 46·2; H, 4·9; N, 13·1. $C_{16}H_{20}O_9N_4$ requires C, 46·6; H, 4·9; N, 13·6%).

Treatment of 1-l-*Arabinosidoglyoxaline*-4 : 5-*dicarboxyamide with Alkaline Potassium Hypobromite*.—The hypobromite solution used in this and the following experiment was prepared by adding bromine (10·7 g.) dropwise to a solution of potassium hydroxide (16·8 g.) in water (100 c.c.) at 0°. The hypobromite content of this solution was estimated by titration with sodium thiosulphate immediately before use. It decomposed very slowly on storing at 0° but more concentrated solutions deteriorated rapidly. The amide (1 g.) was treated with one molecular proportion of the hypobromite solution at 0°, and the solution was kept at 0° for 30 minutes and then heated at 60° for 3 minutes; hypobromite could then no longer be detected. The solution was cooled and acidified to litmus by means of acetic acid. After standing for several days, the amorphous solid which had separated was collected; it gave a positive Molisch test and an insoluble lead salt. When heated, it exhibited marked swelling at 240—245° and more definite decomposition at 260°. Analysis indicated the presence of inorganic matter. Light absorption: (*a*) In N/10-hydrochloric acid; maxima at 2260 A., ε = 6800, and 2637 A., ε = 6400. (*b*) In N/10-sodium hydroxide; maxima at 2415 A., ε = 4900, and 2810 A., ε = 4600.

9-d-*Xylopyranosidoxanthine*.—1-*d*-Xylosidoglyoxaline-4 : 5-dicarboxyamide (1 g.) was treated with alkaline hypobromite solution (6 c.c.) and kept at 0° for 30 minutes and then at 60° for a few minutes until the solution no longer contained hypobromite. The solution was cooled, acidified with acetic acid, and the precipitated solid (0·5 g.) collected. This solid gave a positive Molisch test and an insoluble lead salt. After three crystallisations from water 9-d-*xylopyranosidoxanthine* was obtained as microscopic needles, $[\alpha]_D^{17°}$ − 15° (l = 1, c = 1·4 in water). The crystallisations were attended with much loss of material. 9-*d*-Xylopyranosidoxanthine does not exhibit a definite m. p., but gradually decomposes on heating above 250°; it is quite soluble in water but insoluble in the common organic solvents. For analysis, the air-dried material was further dried at 118°/10^{-3} mm. over phosphoric oxide for 2 hours (Found: C, 41·8; H, 4·6; N, 20·0. $C_{10}H_{12}O_6N_4$ requires C, 42·3; H, 4·2; N, 19·7%). Light absorption: (*a*) In N/10-hydrochloric acid; maxima at 2335 A., ε = 6500, and 2645 A., ε = 8000. (*b*) In N/10-sodium hydroxide; maxima at 2480 A., ε = 7500, and 2805 A., ε = 8000.

Hydrolysis of 9-d-*Xylopyranosidoxanthine*.—The xyloside (0·35 g.) was heated under reflux with aqueous N/2-sulphuric acid (10 c.c.). After a short time xanthine separated and the reaction was complete after 1 hour. The xanthine (0·15 g.) was collected; it was insoluble in water and dilute acids but freely soluble in alkali and dilute aqueous ammonia, separating from the latter on boiling the solution. It decomposed at about 360° (Found: C, 39·2; H, 2·8. Calc. for $C_5H_4O_2N_4$: C, 39·5; H, 2·6%). Light absorption in N/10-sodium hydroxide: maximum at 2845 A., ε = 8000. A specimen of xanthine prepared for comparison by Traube's method (*Ber.*, 1900, **33**, 3045) exhibited a maximum at 2845 A., ε = 8000. The hydrolysis product was further characterised by conversion into its perchlorate, which formed plates which decomposed at 260°.

The filtrate obtained after removal of xanthine was exactly neutralised by addition of sodium hydroxide, and the solution evaporated to dryness. The residue was refluxed with acetic anhydride (4 c.c.) and sodium acetate (0·1 g.) for 1 hour. The product was isolated in the usual manner, and crystallised from aqueous ethanol to give β-tetra-acetyl *d*-xylose as needles, m. p. 124—125° either alone or when mixed with an authentic specimen.

Periodate Oxidations.—The compound (*ca.* 40 mg.) in water (50 c.c.) was treated with sodium metaperiodate solution (0·235M; 10 c.c.), and the solution kept at 20° for 36 hours. A sample of the solution (20 c.c.) was withdrawn and, after the addition of ethylene glycol (1 c.c.) to decompose excess of periodate (which has an acid reaction), titrated against N/100-barium hydroxide solution with methyl-red as indicator. A second sample of the solution (20 c.c.) was made alkaline by addition of sodium bicarbonate solution, and the unchanged metaperiodate estimated in the usual manner.

Compound.	Formic acid (mols. per mol.).	Periodate consumed (mols. per mol.).
1-*d*-Xylosidoglyoxaline-4 : 5-dicarboxyamide	1·01	2·02
9-*d*-Xylosidoxanthine	0·9	1·85
9-Methylxanthine	0	0

It is a pleasure to acknowledge our indebtedness to Dr. A. E. Gillam, who measured the ultra-violet absorption spectra, and to Dr. J. K. N. Jones for assistance with the periodate oxidations.

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[*Received, July 2nd*, 1946.]

77. *Amidines. Part III. Preparation of Substituted Amidines from Ammonium or Substituted Ammonium Salts and* N-*Acylbenzenesulphonalkylamides or Acylbenzenesulphonanilides.*

By P. Oxley and W. F. Short.

Mixed imides, $Ar\cdot SO_2\cdot NX\cdot CO\cdot R$, and ammonium salts, $YZNH_2^{\oplus}A^{\ominus}$, afford salts of amidines, $R\cdot C(:NX)\cdot NYZ$. When Z = H, the main product, $R\cdot C(:NX)\cdot NHY$, is sometimes accompanied by $R\cdot C(:NX)\cdot NHX$ and $R\cdot C(:NY)\cdot NHY$, produced in some instances by disproportionation of the amidine salt first formed, and in others by a series of reactions involving (1) partial aminolysis of the mixed imide, $Ar\cdot SO_2\cdot NX\cdot CO\cdot R$, to $Ar\cdot SO_2\cdot NHX$ and $R\cdot CO\cdot NHY$, (2) formation of $Ar\cdot SO_2\cdot NY\cdot CO\cdot R$ by elimination of $X\cdot NH_2$ (as a salt) from the carbonamide and sulphonamide, (3) reaction of each of the mixed imides with the salts of $X\cdot NH_2$ and of $Y\cdot NH_2$.

In Part II (*J.*, 1946, 763) evidence was advanced to show that the production of amidines from carboxylic acids and sulphonamides involves an exchange of functional groups between the reactants, followed by the formation of a "mixed imide", $R'\cdot SO_2\cdot NH\cdot CO\cdot R$, and its decomposition to a cyanide which is then converted into an amidinium sulphonate by the ammonium sulphonate produced in the second stage of the reaction. When a carboxylic acid was heated with a sulphondialkylamide a carbondialkylamide was produced, and we now find that acids and *N*-monosubstituted sulphonamides (2 mols.) afford *NN'*-disubstituted amidinium sulphonates. We suggest that the reaction takes place in stages as follows:

$$R\cdot CO_2H + R'\cdot SO_2\cdot NHX \longrightarrow R\cdot CO\cdot NHX + R'\cdot SO_2\cdot OH \quad . \quad . \quad . \quad . \quad . \quad (I)$$

$$R\cdot CO\cdot NHX + R'\cdot SO_2\cdot NHX + R'\cdot SO_2\cdot OH \longrightarrow R\cdot CO\cdot NX\cdot SO_2\cdot R' + R'\cdot SO_2\cdot ONH_3X \quad . \quad . \quad (II)$$

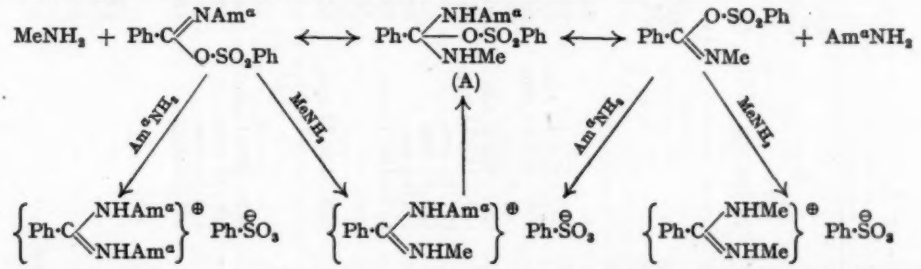
$$R\cdot CO\cdot NX\cdot SO_2R' \longrightarrow R\cdot C(:NX)\cdot O\cdot SO_2\cdot R' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (III)$$

$$R\cdot C(:NX)\cdot O\cdot SO_2R' + R'\cdot SO_2\cdot ONH_3X \longrightarrow R\cdot C(:NX)\cdot NHX,R'\cdot SO_3H + R'\cdot SO_3H \quad . \quad . \quad (IV)$$

Stages I and II are analogous to reactions which were shown to occur with the unsubstituted sulphonamides. The isomerisation III, also analogous to that assumed to occur with the unsubstituted mixed imide, affords a rational explanation of the production of an amidinium salt as the final product. Stage IV, representing the aminolysis of a sulphonic ester by an ammonium sulphonate, receives support from the observation that methyl benzenesulphonate and ammonium benzenesulphonate at 225° afford methylammonium benzenesulphonate and, in a subsequent communication, Stages III and IV will be correlated with the Beckmann transformation. Further, it is now found that a number of substituted mixed imides, $R'\cdot SO_2\cdot NX\cdot CO\cdot R$, prepared from an acid chloride and an *N*-substituted sulphonamide, react with the sulphonic acid salts of ammonia and primary and secondary amines at *ca.* 200° to give $R\cdot C(:NX)\cdot NYZ,R'\cdot SO_3H$. The use of sulphonic acid salts is convenient since both the amidinium salt and the free sulphonic acid produced in the reaction are stable at the temperature employed and the sulphonates are less hygroscopic and more soluble in the melt than other salts. An equivalent quantity of the hydrochloride or the sulphate of the base has been successfully used in a number of cases, and the scope of the method is illustrated by the examples given in the Table. This reaction provides a convenient method for the preparation of a number of *N*-mono- and *NN'*-di-, and tri-substituted amidines, in which the substituents may all be different if desired, some of which cannot be prepared by the Pinner reaction, the imido-chloride method, or the method described in Part I (*J.*, 1946, 147). Methylation of mono- and *NN'*-di-substituted amidines invariably gives a mixture of products, and one of the isomers is usually produced in such small quantity that it could not be prepared economically in this way (see Burtles and Pyman, *J.*, 1923, **123**, 361; Pyman, *ibid.*, pp. 367, 3359); each of the isomers may be obtained with equal ease by heating a mixed imide with the appropriate amine salt.

In normal cases only a single amidine appears to be produced by the interaction of a mixed imide and an ammonium salt, since the crude amidine and/or its salt has almost the optimum melting point and complete purification involves only a small loss. In a few cases (Nos. 14—16, 23, 24) the expected amidine, $Ph\cdot C(:NX)\cdot NHY$, is accompanied by the products of its disproportionation, $Ph\cdot C(:NX)\cdot NHX$ and $Ph\cdot C(:NY)\cdot NHY$. Insufficient examples are at present available to allow the structural factors leading to this disproportionation to be discerned, but it is already clear that a mixture of symmetrical amidines can be produced from the salt of the unsymmetrical amidine initially formed, or, when this is stable at the temperature of the reaction, three amidines may be produced by concurrent reactions which occur at an earlier stage. Thus, when *N-methyl-N'-n-amylbenzamidinium benzenesulphonate* is heated at 200°, *ca.* 70% is recovered unchanged

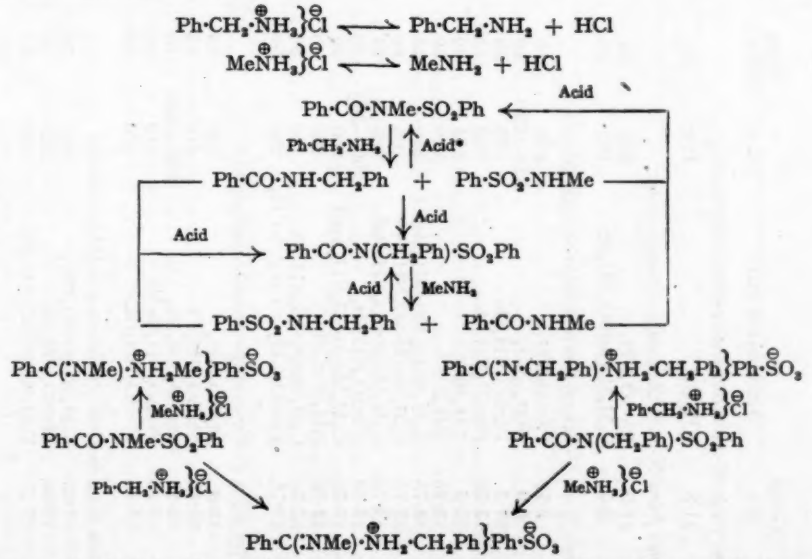
and the rest is converted into the benzenesulphonates of NN′-*dimethylbenzamidine* and NN′-*di*-n-*amylbenzamidine*. A mixture having approximately the same composition is obtained from *N*-*benzoylbenzenesulphonmethylamide* and *n*-amylammonium benzenesulphonate at 200° (No. 14). The mechanism of the disproportionation of the amidinium salt is uncertain, but may involve its conversion into a sulphonic ester (A) decomposing into two different imido-sulphonates and the corresponding amines, which then react to yield three amidinium salts.



So far as we are aware, the only other changes involving the migration of hydrocarbon radicals substituted in the amidino-group concern a number of pairs of isomeric triarylbenzamidines which were shown by Chapman (*J.*, 1929, 2133 and subsequent papers) to afford equilibrium mixtures when the free bases are heated at 300—334°, the rearrangement being an intramolecular process.

$$Ph\cdot C(:NX)\cdot NXY \longleftrightarrow Ph\cdot C(:NY)\cdot NX_2$$

N-Benzoylbenzenesulphonmethylamide also affords a mixture of amidines with benzylammonium chloride (No. 15) and with phenylammonium toluene-*p*-sulphonate (No. 16) but this cannot be due to disproportionation of the amidinium salt initially formed since *N*-benzyl-*N*′-methylbenzamidinium hydrochloride and toluene-*p*-sulphonate and *N*-phenyl-*N*′-methylbenzamidinium benzenesulphonate remain substantially unchanged when heated at 200° for an hour. We suggest that in these cases three amidines are produced by a series of reactions which may be illustrated by reference to the first example (No. 15) as follows. The mixed imide is attacked by benzylamine, resulting from the dissociation of its hydrochloride, with formation of benzbenzylamide and benzenesulphonmethylamide, which, in presence of acid, afford either *N*-benzoylbenzenesulphonbenzylamide and a methylammonium salt or *N*-benzoylbenzenesulphonmethylamide and a benzylammonium salt. Each of these mixed imides then reacts with a methylammonium salt or a benzylammonium salt to give an amidinium salt, so that the composition of the amidine mixture is determined by the following reactions, many of which must reach equilibrium.



* In each case "acid" signifies that the reaction which takes place follows the generalised equation (II).

	Amide (g.).	Ammonium salt.*	Temp.	Time (mins.).	Amidine, R·C(:NX)·NYZ. R.	X.	Y.	Z.	M. p.	B. p.	Yield (%).	Amidine picrate, m. p.
Amidine from **N-*Acetylbenzenesulphonmethylamide*:**												
(1)	21·3	NH_2MeCl	170°	30	Me	Me	Me	H	38—40°	75°/10 mm.	24	132·5°
Amidines from **N-*Acetylbenzenesulphonanilide*:**												
(2)	11·0	$Ph·SO_3NH_4$	200	30	Me	Ph	H	H	—	—	19	188
(3)	5·5	$C_6H_4Me(p)·SO_3NH_3Ph$	180	30	Me	Ph	Ph	H	132·5	—	57	171
Amidines from **N-*Benzoylbenzenesulphonmethylamide*:**												
(4)	2·75	$Ph·SO_3NH_4$	225	15	Ph	Me	H	H	—	—	93	130—131
(5)	6·9	$(NH_4)_2SO_4$	225—230	40	Ph	Me	H	H	—	—	46	130—131
(6)	27·5	$Ph·SO_3NH_3Me$	235	30	Ph	Me	Me	H	81	127—128/11 mm.	97	172—173
(7)	13·75	$Ph·SO_3NH_2Me_2$	200	15	Ph	Me	Me	Me	—	106—107/11 mm.	60·5	137·5
(8)	55·5	NH_2Me_2Cl	205	20	Ph	Me	Me	Me	—	83/2 mm.	62	137·5
(9)	13·75	NH_3EtCl	220	30	Ph	Me	Et	H	63—64	124—126/9 mm.	86·5	168·5—169
(10)	13·75	$C_6H_4Me(p)·SO_3NH_2MeEt$	210	45	Ph	Me	Me	Et	—	115—117/13 mm.	61	101
(11)	13·75	$C_6H_4Me(p)·SO_3NH_3Pr^{\alpha}$	205	60	Ph	Me	Pr^{α}	H	—	137/11 mm.	74	138
(12)	13·75	$C_6H_4Me(p)·SO_3NH_3Pr^{\beta}$	225	30	Ph	Me	Pr^{β}	H	—	119/11 mm.	45·5	174
(13)	13·75	$Ph·SO_3NH_2Et_2$	200—205	20	Ph	Me	Et	Et	—	124/15 mm.	62	150
(14)	13·75	$C_6H_4Me(p)·SO_3NH_3Am^{\alpha}$	200	50	Ph	Me	Am^{α}	H	—	157—159/7 mm.	60	109
(15)	13·75	$NH_3(CH_2Ph)Cl$	200	40	Ph	Me	$Ph·CH_2$	H	—	—	19	121·5—122
(16)	13·75	$C_6H_4Me(p)·SO_3NH_3Ph$	160	30	Ph	Me	Ph	H	135	—	21	169
(17)	13·75	$Ph·SO_3NH_2{<}[CH_2]_4{>}CH_2$	200	30	Ph	Me	$<[CH_2]_4>CH_2$		—	153—155/11 mm.	54	143
Amidines from **N-*Benzoyltoluenesulphonethylamide*:**												
(18)	13·0	$Ph·SO_3NH_4$	225	15	Ph	Et	H	H	—	—	82	145
(19)	15·15	$Ph·SO_3NH_3Et$	210	15	Ph	Et	Et	H	72	102—104/1 mm.	82	185
(20)	15·15	$Ph·SO_3NH_3Me_2$	220—240	15	Ph	Et	Me	Me	—	130/12 mm.	54·5	120·5
(21)	15·15	$Ph·SO_3NH_2MeEt$	210	40	Ph	Et	Me	Et	—	112/11 mm.	53	103·5—104
(22)	15·15	$Ph·SO_3NH_2Et_2$	225	30	Ph	Et	Et	Et	—	121/11 mm.	49	102
Amidines from **N-*Benzoyltoluene*-p-*sulphonanilide*:**												
(23)	17·55	$C_6H_4Me(p)·SO_3NH_4$	225	30	Ph	Ph	H	H	116	—	27	—
(24)	17·55	$Ph·SO_3NH_3Me$	225	15	Ph	Ph	Me	H	135	—	38	169
(25)	17·55	$C_6H_4Me(p)·SO_3NH_3Ph$	190	30	Ph	Ph	Ph	H	147	—	95	221

* 1 Mol. of ammonium salt was used except in the case of ammonium sulphate.

(1) NN′-*Dimethylacetamidinium picrate* separated from *iso*propanol in long daggers, m. p. 132·5° (Found: N, 22·3. $C_{10}H_{13}O_7N_5$ requires N, 22·2%). The *toluene*-p-*sulphonate* crystallised from *iso*propanol in short needles, m. p. 119° (Found: N, 10·8. $C_{10}H_{18}O_3N_2S$ requires N, 10·85%). Pinner (" Die Imidoäther ", p. 112) prepared the hydrochloride, m. p. 218°.

(2) Brunner, Matzler, and Mössmer (*Monatsh.*, 1927, **48**, 125) state that *N*-phenylacetamidinium picrate has m. p. 188·5°. *NN′*-Diphenylacetamidine (7%) was obtained as by-product and had m. p. 131—132°, undepressed on admixture with an authentic specimen.

(3) The reaction was exothermic so that the internal temperature remained at 190° for some minutes. The crude amidine (3·7 g., m. p. 115—125°) was recrystallised from ligroin (b. p. 100—120°), and the pure compound, m. p. 132·5°, did not depress the m. p. of an authentic specimen (Brunner, Matzler, and Mössmer, *loc. cit.*).

(4) Pyman (*J.*, 1923, **123**, 3371) states that the picrate has m. p. 130—132°. N-*Methylbenzamidinium benzenesulphonate* had m. p. 129° (Found: N, 9·5. $C_{14}H_{16}O_3N_2S$ requires N, 9·6%).

(5) *N*-Benzoylbenzenesulphonmethylamide was heated with 0·5 mol. of ammonium sulphate.

(6) Pyman (*loc. cit.*) states that *NN′*-dimethylbenzamidine and its picrate have m. p. 80—81° and 171—172° respectively. The *sulphamate* consisted of long prisms, m. p. 159° (decomp.) (Found: N, 17·05. $C_9H_{13}O_3N_3S$ requires N, 16·75%).

(7) and (8) Dimethylammonium benzenesulphonate had m. p. 116°. Norton and Westenhoff (*Amer. Chem. J.*, 1888, **10**, 130) record m. p. 110°. Pyman (*loc. cit.*) states that *NNN′*-trimethylacetamidinium picrate has m. p. 136—138°. The *benzenesulphonate* had m. p. 156·5° (Found: N, 8·7. $C_{16}H_{20}O_3N_2S$ requires N, 8·75%).

(9) N-*Methyl*-N′-*ethylbenzamidine* was very hygroscopic and had m. p. 63—64° (Found: N, 16·9. $C_{10}H_{14}N_2$ requires N, 17·3%). The *picrate* had m. p. 168·5—169° (Found: N, 17·9. $C_{16}H_{17}O_7N_5$ requires N, 17·9%).

(10) Ethylation of *NN′*-dimethylbenzamidine afforded the same amidine thus confirming the structure. The *picrate* had m. p. 101° (Found: N, 17·2. $C_{17}H_{19}O_7N_5$ requires N, 17·3%) and the *benzenesulphonate* m. p. 121·5—122° (Found: N, 8·4. $C_{17}H_{22}O_3N_2S$ requires N, 8·4%). Methylethylammonium toluene-*p*-sulphonate, m. p. 38—40°, was exceedingly hygroscopic.

(11) n-*Propylammonium toluene*-p-*sulphonate* separated from *iso*propanol in plates, m. p. 139—139·5° (Found: N, 6·2. $C_{10}H_7O_3NS$ requires N, 6·1%). N-*Methyl*-N′-n-*propylbenzamidinium picrate* had m. p. 138° (Found: N, 17·5. $C_{17}H_{19}O_7N_5$ requires N, 17·3%).

(12) iso*Propylammonium toluene*-p-*sulphonate* crystallised in rods, m. p. 128° (Found: N, 6·0. $C_{10}H_{17}O_3NS$ requires N, 6·1%). N-*Methyl*-N′-iso-*propylbenzamidinium picrate* had m. p. 174° (Found: N, 17·5. $C_{16}H_{17}O_7NS$ requires N, 17·3%), and the *benzenesulphonate*, m. p. 161—161·5° (Found: N, 8·3. $C_{17}H_{22}O_3N_2S$ requires N, 8·4%).

(13) N-*Methyl*-N′N′-*diethylbenzamidinium picrate* had m. p. 150° (Found: N, 16·9. $C_{18}H_{21}O_7N_5$ requires N, 16·7%), and the *benzenesulphonate*, m. p. 114° (Found: N, 8·0. $C_{18}H_{24}O_3N_2S$ requires N, 8·05%).

(14) N-*Methyl*-N′-n-*amylbenzamidinium picrate* had m. p. 109° (Found: N, 16·35. $C_{19}H_{22}O_7N_5$ requires N, 16·2%). *NN′*-Dimethylbenzamidine (17%) and *NN′*-di-*n*-amylbenzamidine (12%) were also produced (see below).

(15) *N*-Benzyl-*N′*-methylbenzamidinium picrate had m. p. 121·5—122° (Found: N, 15·6. Calc. for $C_{21}H_{19}O_7N_5$: N, 15·45%). Pyman (*J.*, 1923, **123**, 3359) records m. p. 118—122°. *NN′*-Dibenzylbenzamidine (29%) was also formed (see below).

(16) *NN′*-Diphenylbenzamidine, m. p. and mixed m. p. 147°, was also produced (5·4 g. or 40%). *NN′*-Dimethylbenzamidine would not have been detected by the method used for isolating the products.

(17) *Piperidinium benzenesulphonate* separated from acetone in hygroscopic prisms, m. p. 88° (Found: N, 5·8. $C_{11}H_{17}O_3NS$ requires N, 5·8%). A by-product of the amidine reaction (3·8 g.), b. p. 178—182°/11 mm., was not investigated. N-*Methyl*-N′N′-*pentamethylenebenzamidinium picrate* had m. p. 143° (Found: N, 16·3. $C_{19}H_{21}O_7N_5$ requires N, 16·2%), and the *benzenesulphonate*, m. p. 166° (Found: N, 7·7, 7·7. $C_{19}H_{24}O_3N_2S$ requires N, 7·8%.)

(18) N-*Ethylbenzamidinium picrate* had m. p. 145° (Found: N, 18·6. $C_{15}H_{15}O_7N_5$ requires N, 18·6%), and the *benzenesulphonate*, m. p. 162·5—163° (Found: N, 9·2. $C_{15}H_{16}O_3N_2S$ requires N, 9·15%).

(19) Ethylammonium benzenesulphonate had m. p. 101°. Norton and Westenhoff (*loc. cit.*) record m. p. 92°. NN′-*Diethylbenzamidine* was very hygroscopic (Found: N, 15·3. $C_{11}H_{16}N_2$ requires N, 15·9%), the *picrate* had m. p. 185° (Found: N, 17·25. $C_{17}H_{19}O_7N_5$ requires N, 17·3%), and benzoylation afforded *N*-benzoyl-*NN′*-diethylbenzamidine, m. p. 91° (Found: N, 9·9. Calc. for $C_{18}H_{20}ON_2$: N, 10·0%). Lander (*J.*, 1903, **83**, 320) states that this benzoyl derivative has m. p. 90—91·5°.

(20) *NN*-Dimethyl-*N′*-ethylbenzamidine afforded a *picrate*, m. p. 120·5° (Found: N, 17·3. $C_{17}H_{19}O_7N_5$ requires N, 17·3%), and a *benzenesulphonate*, m. p. 138° (Found: N, 8·4. $C_{17}H_{22}O_3N_2S$ requires N, 8·4%).

(21) Methylation of *NN′*-diethylbenzamidine afforded the same amidine thus confirming the structure. N-*Methyl*-NN′-*diethylbenzamidinium picrate* had m. p. 103·5—104° (Found: N, 16·8. $C_{19}H_{21}O_7N_5$ requires N, 16·7%).

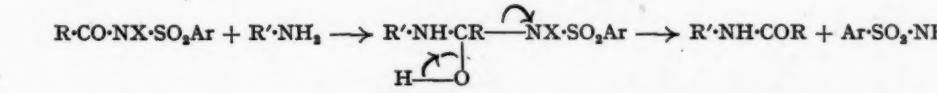
(22) *NNN′*-Triethylbenzamidine afforded a *picrate*, m. p. 102° (Found: N, 16·1. $C_{19}H_{23}O_7N_5$ requires N, 16·2%), and a *benzenesulphonate*, m. p. 104—105° (Found: N, 7·7. $C_{19}H_{26}O_3N_2S$ requires N, 7·7%).

(23) Brunner, Seeger, and Dittrich (*Monatsh.*, 1924, **45**, 69) state that *N*-phenylbenzamidine has m. p. 113·5°; Oxley and Short (*J.*, 1946, 147) record m. p. 116°. *NN′*-Diphenylbenzamidine (8·5%) was produced as by-product (see below).

(24) Pyman (*loc. cit.*, p. 368) states that *N*-phenyl-*N′*-methylbenzamidine has m. p. 135—136°. *NN′*-Dimethylbenzamidine (7%) and *NN′*-diphenylbenzamidine (22%) are produced as by-products (see below).

(25) Busch and Falco (*Ber.*, 1910, **43**, 2559) state that *NN′*-diphenylbenzamidine has m. p. 144°.

The fission of *N*-benzoylbenzenesulphonmethylamide by amines postulated above has been confirmed in two cases. Thus, the mixed imide and benzylamine at 230° afford benzenesulphonmethylamide and benzbenzylamide, each in 88% yield, whilst aniline at 245° yields benzanilide (88%), benzenesulphonmethylamide (64%), and *N*-phenyl-*N'*-methylbenzamidinium benzenesulphonate (4%). The presence of an additional basic centre in the molecule of the salt can also lead to fission of the mixed imide; thus *N*-benzoylbenzenesulphonmethylamide and *2-aminopyridine toluene*-p-*sulphonate* afford benzenesulphonmethylamide and 2-benzamidopyridine. Similarly, whilst N-*benzoylbenzenesulphon-2-pyridylamide* is converted into N-2-*pyridyl*-N'-*methylbenzamidine* (60%) by methylammonium benzenesulphonate (1 mol.) at 200°, 2-aminopyridine toluene-*p*-sulphonate (1 mol.) produces 2-benzamidopyridine (*ca.* 100%) and 2-benzenesulphonamidopyridine (77%). Addition of acid, by increasing the degree of neutralisation of the basic centres in the aminopyridine, should promote the formation of amidine and hinder aminolysis of the mixed imide to a sulphonamide and a carbonamide. In agreement with this deduction, equimolecular quantities of *N*-benzoylbenzenesulphon-2-pyridylamide, 2-aminopyridine benzenesulphonate, and benzenesulphonic acid afford NN'-*di*-(2-*pyridyl*)*benzamidine* (17·5%), 2-benzamidopyridine (52%), and 2-benzenesulphonamidopyridine (46%) when heated at 200°. It is probable that fission of a mixed imide by an amine involves addition at the carbonyl group as follows:



We find that dibenzoylmethylamine and methylammonium benzenesulphonate at 210° afford *NN'*-dimethylbenzamidinium benzenesulphonate (49%), and it seems probable that this reaction involves isomerisation of the diacylamine to Ph·CO·O·CPh:NMe, which then reacts with the substituted ammonium salt (cf. equations III and IV above). A diacylamine may also function as an intermediate in the production of an *NN'*-disubstituted amidine from an acid and an *N*-monosubstituted sulphonamide, but could not be involved in the formation of amidines from mixed imides except where the imide undergoes fission and a mixture of amidines results.

In view of the production of amidines from *N*-substituted mixed imides and ammonium benzenesulphonate, it seemed possible that amidines could be produced directly from imides of the type R'·SO_2·NH·CO·R, rather than by decomposition to a cyanide which then reacts with the ammonium salt (Part II). Investigation of this point in the case of *N-p*-methylsulphonylbenzoylbenzenesulphonamide and ammonium benzenesulphonate showed that after two hours at 190—195°, the lowest temperature required to produce a change, the main product is *p*-cyanophenyl methyl sulphone, and the trace of amidine (Fuller reaction) simultaneously formed is no more than could be accounted for by the interaction of the cyanide and the ammonium salt at that temperature.

The interaction of *N*-acylbenzenesulphonalkylamides with the salts of diamines will be described in a later communication.

Experimental.*

NN'-*Dimethylbenzamidine.*—(1) *From benzoic acid.* Benzoic acid (12·2 g.) and benzenesulphonmethylamide (36 g.; 1·2 mols.) reacted exothermally at 235°, the temperature rising to 270°. The product dissolved completely in water and required one equivalent of sodium hydroxide for neutralisation to Congo-red. The liquid was made strongly alkaline and extracted with chloroform, the extract (13·5 g.) giving the following fractions on distillation. (*a*) B. p. 127—128°/11 mm., m. p. 70—75°. Recrystallisation from benzene–light petroleum (1 : 1) afforded *NN'*-dimethylbenzamidine, m. p. and mixed m. p. 81°. Yield, 12·1 g. (82%). (*b*) B. p. 126—128°/2 mm. This fraction had m. p. 78—79°, undepressed by admixture with benzmethylamide. Yield, 1·2 g. It is probable that this compound was produced by hydrolysis of the amidine, rather than by functional exchange between benzoic acid and benzenesulphonmethylamide.

(2) *From benzmethylamide.* (*a*) A mixture of benzmethylamide (10·1 g.) and anhydrous benzenesulphonic acid (11·85 g.; 1 mol.) was heated at 225° for 30 minutes, and then cooled, diluted with water (100 c.c.), and extracted with chloroform. Benzoic acid (3·8 g. or 83%), m. p. and mixed m. p. 121°, was isolated from the chloroform solution. The aqueous solution, which contained acid equivalent to 0·7 mol. (Congo-red), was made strongly alkaline and extracted with chloroform to which it yielded *NN'*-dimethylbenzamidine, m. p. 74—77° (2·65 g. or 48%). One crystallisation raised the m. p. to 81°, undepressed on admixture with an authentic specimen.

(*b*) An equimolecular mixture of benzmethylamide (3·4 g.), benzenesulphonmethylamide (4·3 g.), and benzenesulphonic acid (4·0 g.), heated at 220—225° for 30 minutes, afforded crude *NN'*-dimethylbenzamidine, m. p. 75—77° (3·5 g., 94%). Recrystallisation raised the m. p. to 81°, and the

* See also Boots Pure Drug Co., Oxley and Short, B.P.Appln., 9288/13.4.1945.

benzenesulphonate had m. p. 104°, either alone or after admixture with an authentic specimen of *NN'*-dimethylbenzamidinium benzenesulphonate. An attempt to isolate *N*-benzoylbenzenesulphonmethylamide by conducting the reaction at a lower temperature was unsuccessful.

(3) *From dibenzoylmethylamine.* Dibenzoylmethylamine (4·78 g.) and methylammonium benzenesulphonate (4 g.; 1·1 mol.) were heated at 210° for an hour and the strongly acid product was dissolved in water, made strongly alkaline, and extracted with chloroform. Evaporation of the solvent gave crude *NN'*-dimethylbenzamidine (1·4 g., 47%) which was converted into the picrate, m. p. and mixed m. p. 172—173° (2·45 g. or 32·5%), when added to a solution of picric acid (2·5 g.) in methanol. When the mixture was heated for an hour at 225° the yields of crude amidine and picrate were 49 and 36% respectively.

Preparation of N-*Acylbenzenesulphonalkylamides and* N-*Acylbenzenesulphonanilides.*

N-*Acetylbenzenesulphonmethylamide.*—Addition of a solution of potassium hydroxide (35 g.; 1·05 mol.) in hot methanol (100 c.c.) to benzenesulphonmethylamide (85·5 g.) in hot *iso*propanol (100 c.c.) and cooling to 0° afforded the potassium salt (100 g. or 96%). A solution of acetyl chloride (39 g.; 1 mol.) in benzene (50 c.c.) was added to the potassium salt suspended in benzene (200 c.c.) and the mixture boiled for 10 minutes, cooled, washed with water and dilute sodium hydroxide, dried, and evaporated. Distillation of the residue afforded N-*acetylbenzenesulphonmethylamide* as a colourless oil, b. p. 130°/0·7 mm. (Found: C, 50·3; H, 5·2; N, 6·5. $C_9H_{11}O_3NS$ requires C, 50·7; H, 5·2; N, 6·6%). Yield, 90·4 g. (89%).

N-*Acetylbenzenesulphonanilide.*—Acetyl chloride (14·5 g.; 1 mol.) was added dropwise to a mixture of benzenesulphonanilide (43 g.) and pyridine (30 c.c.; 2 mols.), and the semi-solid mass was heated on the steam-bath for ½ hour. The solid obtained after shaking with dilute hydrochloric acid was recrystallised from 80% aqueous alcohol (200 c.c.) to give elongated plates, m. p. 115·5°. Wheeler, Smith, and Warren (*Amer. Chem. J.*, 1897, **19**, 760) record m. p. 116·5°.

N-*Benzoylbenzenesulphonmethylamide.*—Benzmethylamide, benzenesulphonyl chloride, and pyridine afforded a neutral oil which slowly dissolved in water to a strongly acid solution and was probably the benzenesulphonic ester of the *iso*amide, $PhSO_3{\cdot}O{\cdot}CPh{:}NMe$. A mixture of benzenesulphonmethylamide (35 g.), benzoyl chloride (28·8 g.; 1 mol.), and pyridine (16 c.c.; 1 mol.) was heated on the steam-bath for 14 hours, diluted with chloroform, and shaken with water and dilute sodium hydroxide. Distillation of the chloroform solution afforded N-*benzoylbenzenesulphonmethylamide* as a colourless oil, b. p. 200°/2 mm., which quickly solidified and separated from methanol in colourless plates, m. p. 89·5° (Found: N, 5·2. $C_{14}H_{13}O_3NS$ requires N, 5·1%). Yield, 51 g. (90%).

N-*Benzoyltoluene*-p-*sulphonethylamide*, prepared in the same way from toluene-*p*-sulphonethylamide, benzoyl chloride, and pyridine, separated from methanol in colourless prisms, m. p. 51° (Found: N, 4·6. $C_{16}H_{17}O_3NS$ requires N, 4·6%).

N-*Benzoyltoluene*-p-*sulphonanilide.*—Toluene-*p*-sulphonyl chloride (95 g.; 1 mol.) was added to aniline (46·5 g.) and pyridine (150 c.c.) so that the temperature remained below 60°. Subsequent addition of benzoyl chloride (70 g.; 1 mol.) to the reddish-brown mixture produced an almost colourless solution which soon solidified. After 45 minutes' heating on the steam-bath, the solid was collected and crystallised from alcohol, to give colourless prisms, m. p. 150—151°. Yield, 122 g. (69·5%). Remsen and Palmer (*Amer. Chem. J.*, 1886, **8**, 242) prepared *N*-benzoyltoluene-*p*-sulphonanilide from toluene-*p*-sulphonanilide and benzoyl chloride at 140° and record m. p. 149° (corr.).

N-*Benzoylbenzenesulphon*-2-*pyridylamide.*—The potassium salt of 2-benzenesulphonamidopyridine was obtained in 97% yield by dissolving 2-benzenesulphonamidopyridine (46·8 g.) (English, Chappell, Bell, and Roblin, *J. Amer. Chem. Soc.*, 1942, **64**, 2516) and potassium hydroxide (15 g.; 1·1 mol.) in warm methanol (50 c.c.), diluting the solution with *iso*propanol (100 c.c.), and collecting the colourless needles (53 g.) which separated on cooling. A suspension of the potassium salt in benzene (250 c.c.) was boiled with benzoyl chloride (28 g.) for 4 hours, and the resulting solid collected, washed with water, and dried. N-*Benzoylbenzenesulphon*-2-*pyridylamide* was obtained in colourless plates (54 g. or 82%), m. p. 175—176° (Found: N, 8·5. $C_{18}H_{14}O_3N_2S$ requires N, 8·3%). Benzoyl chloride, 2-benzenesulphonamidopyridine, and pyridine afforded an unstable compound which was probably 1-benzoyl-2-benzenesulphonimido-1 : 2-dihydropyridine.

Fission of N-*Benzoylbenzenesulphonmethylamide by Amines.*—(1) *By aniline.* A mixture of *N*-benzoylbenzenesulphonmethylamide (13·75 g.) and aniline (4·65 g.; 1 mol.) was heated at 245—250° for 30 minutes. The powdered reaction product was extracted with warm water (100 c.c.); the solution deposited almost pure *N*-phenyl-*N'*-methylbenzamidine, m. p. 133° (0·4 g. or 3·85%), on being made alkaline. Benzenesulphonmethylamide (5·5 g. or 64%) was extracted from the solid with dilute aqueous sodium hydroxide; the residue (10·1 g.) afforded benzanilide, m. p. and mixed m. p. 163° (8·7 g. or 88·5%), when crystallised from alcohol.

(2) *By benzylamine.* An equimolecular mixture of *N*-benzoylbenzenesulphonmethylamide (5·50 g.) and benzylamine (2·14 g.) was heated at 230—235° for an hour, and the cooled product was dissolved in benzene. The benzene solution yielded benzenesulphonmethylamide (3·0 g., 88%) to dilute sodium hydroxide solution, and removal of most of the benzene and trituration of the residue with light petroleum gave benzbenzylamide, m. p. 103—104° (3·7 g., 88%). Crystallisation from benzene–light petroleum raised the m. p. to 105·5—106°, in agreement with the value recorded by Beckmann (*Ber.*, 1890, **23**, 3334). Dilute acetic acid removed basic material (0·1 g.) from the original mother liquor, evaporation then gave unchanged benzoylbenzenesulphonmethylamide (0·5 g. or 9%), which had m. p. 89° after crystallisation from methanol.

(3) *By* 2-*aminopyridine toluene*-p-*sulphonate.* Equimolecular quantities of 2-aminopyridine and anhydrous toluene-*p*-sulphonic acid in *iso*propanol afforded 2-*aminopyridine toluene*-p-*sulphonate*, m. p. 133° (Found: N, 10·7. $C_{18}H_{14}O_3N_2S$ requires N, 10·5%). A mixture of this salt (13·3 g.; 1 mol.) with *N*-benzoylbenzenesulphonmethylamide (13·75 g.) was heated at 230° for 30 minutes, and the cold melt dissolved in water. The solution was decolorised with charcoal, made alkaline with aqueous sodium

hydroxide, and extracted with chloroform. Distillation of the extract (9·9 g.) gave (*a*) 2-aminopyridine, b. p. 100—120°/11 mm. (1·2 g.; 25%), identified as picrate, m. p. and mixed m. p. 223°; (*b*) a fraction (7·0 g.), b. p. 143—145°/1 mm.; and (*c*) a small dark residue. Fraction (*b*) afforded colourless needles, m. p. 81·5°, on recrystallisation from light petroleum (b. p. 100—120°) and was identified as 2-benzamidopyridine (Found: N, 14·2. Calc. for $C_{12}H_{10}ON_2$: N, 14·1%) by comparison with a sample prepared as described by Tschitschibabin and Bylinkin (*Ber.*, 1922, **55**, 1000) who record m. p. 87°. The picrate, prepared from material obtained by either method, had m. p. 199° (Found: N, 16·5. Calc. for $C_{18}H_{13}O_9N_5$: N, 16·4%), whereas Tschitschibabin and Bylinkin (*loc. cit.*) record m. p. 193°. The *benzenesulphonate* had m. p. 130° (Found: N, 8·0. $C_{18}H_{16}O_4N_2S$ requires N, 7·9%). The distillation residue (*c*) and picric acid afforded 2-benzamidopyridine picrate, m. p. and mixed m. p. 199° (1·2 g.), making the total yield of 2-benzamidopyridine 76%.

Preparation of Amidines from N-*Acylbenzenesulphonalkylamides and* N-*Acylbenzenesulphonanilides.*

The reactants were heated, preferably with stirring, under the conditions specified in the Table. The methods used for the isolation of the amidines are illustrated by reference to the following cases in which some exceptional features necessitate a detailed description of the procedure.

N-*Methyl*-N′-n-*amylbenzamidine*.—An equimolecular mixture of *N*-benzoylbenzenesulphonmethylamide (13·75 g.) and *n*-amylammonium toluene-*p*-sulphonate (12·95 g.) was heated at 200° for 50 minutes, cooled, and dissolved in chloroform (50 c.c.). An aqueous extract (100 c.c.) of this chloroform solution afforded *NN*′-dimethylbenzamidine, m. p. and mixed m. p. 81° (1·25 g. or 17%), when made strongly alkaline and extracted with chloroform. The amidine salts in the original chloroform solution were decomposed by shaking it with 5N-sodium hydroxide, and the liberated amidines were separated by fractional distillation. The fraction, b. p. 155—160°/7 mm. (mainly 157—159°/7 mm.), gave *N*-methyl-*N*′-*n*-amylbenzamidine (6·1 g. or 60%), which was characterised as the picrate, m. p. 109° (see Table, No. 14). The portion, b. p. 175—180°/7 mm. (mainly 176—177°/7 mm.) (1·6 g., 12%), consisted of NN′-*di*-n-*amylbenzamidine* (Found: N, 10·8. $C_{17}H_{28}N_2$ requires N, 10·8%), and was characterised as the *picrate*, m. p. 83° (Found: N, 14·6. $C_{23}H_{31}O_7N_5$ requires N, 14·3%).

N-*benzyl*-N′-*methylbenzamidine*.—*N*-Benzoylbenzenesulphonmethylamide (13·75 g.) and benzylammonium chloride (7·2 g.; 1 mol.) were heated at 200° for 40 minutes, and the oil which separated when the product was shaken with water was collected in benzene. The aqueous solution was made alkaline and extracted with chloroform, and the gum (2·1 g. or 19%) which remained after removal of the solvent was converted into *N*-benzyl-*N*′-methylbenzamidinium picrate, m. p. 121·5—122° (see No. 15). The benzene solution afforded *NN*′-dibenzylbenzamidine (4·4 g. or 29%) which was converted into the picrate, m. p. 145° (Found: N, 13·1. Calc. for $C_{27}H_{23}O_7N_5$: N, 13·2%). Pyman (*J.*, 1923, **123**, 3373) states that *NN*′-dibenzylbenzamidinium picrate has m. p. 146—147° (corr.).

N-*Phenyl*-N′-*methylbenzamidine*.—(1) The product obtained by heating an equimolecular mixture of *N*-benzoylbenzenesulphonmethylamide (13·75 g.) and aniline toluene-*p*-sulphonate (13·25 g.) at 155—160° for an hour was dissolved in benzene (50 c.c.) and the solution extracted with water (4 × 50 c.c.). The aqueous solution afforded *N*-phenyl-*N*′-methylbenzamidine, m. p. and mixed m. p. 135° (2·2 g. or 21%), further identified as the picrate, m. p. 168—169°, and benzenesulphonate, m. p. 143°, which did not depress the m. p.'s of authentic specimens. The benzene solution was shaken with 2N-sodium hydroxide and concentrated to give *NN*′-diphenylbenzamidine, m. p. and mixed m. p. 147° (5·4 g., 40%). (2) *N*-Benzoyltoluene-*p*-sulphonanilide (17·55 g.) and methylammonium benzenesulphonate (9·5 g.; 1 mol.) exhibited a slightly exothermic reaction when heated at 225°; after 15 minutes at this temperature, the mixture was cooled and shaken with chloroform and aqueous sodium hydroxide. Distillation of the mixed amidines afforded *NN*′-dimethylbenzamidine, b. p. 74—76°/1 mm., m. p. and mixed m. p. 80—81° (0·5 g., 7%), and the residue was neutralised with hydrochloric acid. The sparingly soluble salt which separated was decomposed with alkali giving *NN*′-diphenylbenzamidine, m. p. and mixed m. p. 147° (3 g. or 22%), and the base, precipitated by adding alkali to the mother liquors, afforded *N*-phenyl-*N*′-methylbenzamidine, m. p. and mixed m. p. 135° (4 g., 38%), after crystallisation from benzene.

N-*Phenylbenzamidine*.—*N*-Benzoyltoluene-*p*-sulphonanilide (17·55 g.) and ammonium toluene-*p*-sulphonate (9·5 g.; 1 mol.) were heated at 225° for 30 minutes and the product was shaken with chloroform and 5N-sodium hydroxide. The dark oil (7·6 g.) obtained from the chloroform solution was dissolved in benzene, and the solution shaken with N-hydrochloric acid (40 c.c.) and filtered to remove the solid. Trituration of this solid with aqueous sodium carbonate afforded *NN*′-diphenylbenzamidine, m. p. and mixed m. p. 146—147° (1·15 g., 8·5%). The aqueous portion of the filtrate gave *N*-phenylbenzamidine, m. p. 113—115° (2·65 g. or 27%), on being made alkaline with aqueous sodium carbonate; crystallisation from petroleum (b. p. 100—120°) raised the m. p. to 116°, undepressed on admixture with an authentic specimen.

N-2-*Pyridyl*-N′-*methylbenzamidine*.—*N*-Benzoylbenzenesulphon-2-pyridylamide (8·45 g.) was heated with methylammonium benzenesulphonate (4·73 g.; 1 mol.) at 197° for an hour. The product was dissolved in water (50 c.c.), made strongly alkaline with 5N-sodium hydroxide (30 c.c.), and extracted with chloroform. Distillation of the extract yielded N-2-*pyridyl*-N′-*methylbenzamidine* as a pale yellow gum, b. p. 180—182°/2·5 mm. (3·15 g., 58·5%), which separated from light petroleum (b. p. 80—100°) in colourless rhombic crystals, m. p. 101° (Found: C, 73·6; H, 6·1; N, 19·7. $C_{13}H_{13}N_3$ requires C, 73·9; H, 6·2; N, 19·9%). The *picrate* separated from methanol in rectangular plates, m. p. 180° (Found: N, 19·2. $C_{19}H_{16}O_7N_6$ requires N, 19·1%).

NN′-*Di*-2-*pyridylbenzamidine*.—An equimolecular mixture of *N*-benzoylbenzenesulphon-2-pyridylamide (8·45 g.), 2-aminopyridine benzenesulphonate (6·3 g.), and benzenesulphonic acid (4 g.) was heated at 200° for an hour, and the cold melt was then stirred with water, made strongly alkaline with 5N-sodium hydroxide, and extracted with chloroform. The aqueous solution afforded a precipitate of 2-benzenesulphonamidopyridine, m. p. and mixed m. p. 173—174° (2·7 g.; 46%), on neutralisation with

hydrochloric acid. The residue (5·1 g.) obtained by removing the chloroform was recrystallised from benzene, and gave colourless prisms (1·4 g. or 17·5%) of NN′-*di*-2-*pyridylbenzamidine*, m. p. 175° (Found: N, 20·3. $C_{17}H_{14}N_4$ requires N, 20·4%). 2-Benzamidopyridine, m. p. and mixed m. p. 81·5° (2·6 g. or 52%), was obtained by evaporating the benzene mother liquors and crystallising the residue from light petroleum. Under the same conditions, *N*-benzoylbenzenesulphon-2-pyridylamide (8·45 g.) and 2-aminopyridine toluene-*p*-sulphonate (6·65 g.) afforded only 2-benzenesulphonamidopyridine (77%) and 2-benzamidopyridine (*ca.* 100%).

Action of Heat on some Amidinium Salts.

N-*Methyl*-N′-n-*amylbenzamidine*.—Benzmethylamide imidochloride and *n*-amylamine in ether afforded a gummy hydrochloride which was converted into N-*methyl*-N′-n-*amylbenzamidinium picrate*, m. p. 108° (Found: N, 16·3. $C_{19}H_{23}O_7N_5$ requires N, 16·2%). N-*Methyl*-N′-n-*amylbenzamidine* crystallised in colourless needles, m. p. 40° (Found: N, 13·6. $C_{13}H_{20}N_2$ requires N, 13·7%). The benzenesulphonate was a viscous oil which did not crystallise. The benzenesulphonate (9 g.) was heated at 200° for an hour, and a solution of the cooled melt in chloroform (25 c.c.) was extracted with water (150 c.c.). The base (0·8 g.), obtained from the aqueous solution by making alkaline and extracting with chloroform, was recrystallised from light petroleum (b. p. 60—80°) and gave colourless rectangular plates of *NN′*-dimethylbenzamidine, m. p. 80—81°, converted into its picrate, m. p. 172—173°. Admixture of these preparations with authentic specimens produced no depression in m. p. Distillation of the chloroform extract after making alkaline gave *N*-methyl-*N′*-*n*-amylbenzamidine, b. p. 92°/0·3 mm., m. p. and mixed m. p. 39—40° (3·5 g.), and the residue was converted into a mixture of picrates separated by fractional crystallisation into *N*-methyl-*N′*-*n*-amylbenzamidinium picrate, m. p. and mixed m. p. 105—107° (0·5 g.), and *NN′*-di-*n*-amylbenzamidinium picrate, m. p. 80—83° (1·1 g.), raised to 83° by recrystallisation and undepressed on admixture with an authentic specimen. That is, *N*-methyl-*N′*-*n*-amylbenzamidine, *NN′*-dimethylbenzamidine, and *NN′*-di-*n*-amylbenzamidine were isolated from the product in 74, 11, and 9% yield respectively.

N-*Benzyl*-N′-*methylbenzamidine*.—Benzmethylamide (45 g.) and phosphorus pentachloride (70 g.; 1·01 mol.) gave a 64% yield of the imidochloride when brought into reaction as described by v. Pechmann (*Ber.*, 1895, **28**, 2367), and addition of a solution of benzylamine (22·7 g.) in ether (50 c.c.) to the imidochloride (32·6 g.) in ether (50 c.c.) afforded crude *N*-benzyl-*N′*-methylbenzamidinium chloride, m. p. 160—170° (47 g. or 85%), after being washed with acetone. Traces of benzylammonium chloride were removed by liberating the base and crystallising it from light petroleum (b. p. 60—80°); it was then obtained in needles, m. p. 73°. Pyman (*J.*, 1923, **123**, 3374) states that *N*-benzyl-*N′*-methylbenzamidine has m. p. 71—73° and the picrate m. p. 118—122°, and that the hydrochloride does not crystallise. We obtained a picrate, m. p. 121·5—122°, and the hydrochloride, obtained from hydrogen chloride and a solution of the base in *iso*propanol, had m. p. 180·5—181° (Found: N, 10·5. $C_{15}H_{17}N_2Cl$ requires N, 10·7%). The *toluene-p-sulphonate* had m. p. 123° (Found: N, 7·2. $C_{22}H_{24}O_3N_2S$ requires N, 7·1%). When the hydrochloride (10 g.) was heated at 200° for an hour and then cooled and powdered, it had m. p. 180·5—181° and afforded a quantitative yield of the free base, m. p. 72—73° (8·6 g.), with alkali. The toluene-*p*-sulphonate was maintained at 200° for an hour, cooled, dissolved in chloroform, and shaken with water (30 c.c.). The chloroform solution, when shaken with alkali, dried, and evaporated, afforded 5·6 g. of unchanged amidine, m. p. and mixed m. p. 73°. The aqueous layer, which would have contained *NN′*-dimethylbenzamidine, afforded 0·05 g. of base with alkali, and, when mixed with an equivalent of picric acid in ether, afforded a picrate, m. p. 113—117°, raised to 120—122° by crystallisation from *iso*propanol and unchanged on admixture with *N*-benzyl-*N′*-methylbenzamidinium picrate.

N-*Phenyl*-N′-*methylbenzamidine*.—This amidine was obtained in 83% yield from benzmethylamide imidochloride and aniline (v. Pechmann, *Ber.*, 1897, **30**, 1782; Pyman, *J.*, 1923, **123**, 3366). The *hydrochloride* separated from *iso*propanol as a colourless powder, m. p. 213° (Found: N, 11·3. $C_{14}H_{15}N_2Cl$ requires N, 11·4%), and the *benzenesulphonate* had m. p. 143° (Found: N, 7·8. $C_{20}H_{20}O_3N_2S$ requires N, 7·6%). When the benzenesulphonate (7·36 g.) was heated at 200° for an hour and the product was crystallised from *iso*propanol (10 c.c.), the bulk of the salt (7 g.) was recovered unchanged, m. p. and mixed m. p. 143°. Addition of ether to the filtrate afforded a second crop, m. p. 142·5—143° (0·26 g.), making the total recovery 98·6%. When *N*-phenyl-*N′*-methylbenzamidinium chloride was heated at 220° for 30 minutes, the m. p. of the product was 208—210°, indicating that very little change had taken place.

Methylammonium Benzenesulphonate.—There was no reaction between methyl benzenesulphonate (7·8 g.) and ammonium benzenesulphonate (8·75 g.; 1·2 mols.) at 140°, but after an hour at 225° the product contained methylammonium benzenesulphonate. The product was triturated with a mixture of acetone (20 c.c.) and ether (80 c.c.), and the residual solid, m. p. 200—220° (6·5 g.), was extracted in a Soxhlet apparatus with chloroform. The undissolved solid consisted of crude ammonium benzenesulphonate, m. p. 275—280°, and the chloroform solution deposited crude methylammonium benzenesulphonate (1·9 g., 24%), which afforded the pure salt, m. p. and mixed m. p. 165°, on crystallisation from *iso*propanol (Found: N, 7·4. Calc. for $C_7H_{11}O_3NS$: N, 7·4%). Norton and Westenhoff (*Amer. Chem. J.*, 1888, **10**, 130) state that methylammonium benzenesulphonate has m. p. 147°.

Methyl toluene-*p*-sulphonate (18·6 g.) and ethylammonium chloride (8·15 g.) at 120—150° gave methyl chloride and ethylammonium toluene-*p*-sulphonate, m. p. 113—115°, which crystallised from *iso*propanol in needles, m. p. and mixed m. p. 118° (Norton and Otten, *Amer. Chem. J.*, 1888, **10**, 140, give m.p. 111°) (Found: N, 6·45. Calc. for $C_9H_{13}O_3NS$: N, 6·45%). The yield was 19·6 g. (90%).

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[*Received, June 18th*, 1946.]

78. *Amidines. Part IV. Preparation of Amidines from Cyanides and Ammonium Thiocyanate or Substituted Ammonium Thiocyanates.*

By M. W. Partridge and W. F. Short.

Amidines and *N*-substituted amidines may be prepared by heating cyanides with ammonium or alkylammonium thiocyanates at *ca.* 180°. The yields are sometimes higher than those obtained with ammonium sulphonates.

The preparation of amidines from cyanides and ammonium or substituted ammonium sulphonates was described by Oxley and Short (*J.*, 1946, 147) and we now find that some amidines can be obtained in better yield by heating a cyanide with the more readily available ammonium thiocyanate. The scope of the method is illustrated by the examples given in the table, and attention is directed to a few matters of general interest arising from them. Systematic experiments on the preparation of p-*amidinophenyl methyl sulphone*, recorded in the experimental section, show that the yield of amidine (*a*) increases with increase in the ratio of ammonium thiocyanate to cyanide, the optimum quantity of thiocyanate for preparative purposes being *ca.* 4 mols., and (*b*) is considerably decreased by relatively small variations from the temperature and time of reaction found to give the best results. Part of the ammonium thiocyanate is converted into thiourea, and we find that the *thiocyanate* of *p*-amidinophenyl methyl sulphone is decomposed into *p*-cyanophenyl methyl sulphone to the extent of 47% in 5 minutes at 225°, so that the composition of the reaction product is determined by a number of concurrent reactions. The amidine is also obtained by heating the cyanide with thiourea and, since the yields are considerably lower than those obtained under identical conditions with an equivalent quantity of ammonium thiocyanate, it seems that isomerisation of thiourea to ammonium thiocyanate must precede the production of amidine. Reynolds and Werner (*J.*, 1903, **83**, 1) and Atkins and Werner (*J.*, 1912, **99**, 1172) showed that equilibrium between ammonium thiocyanate and thiourea is reached somewhat slowly at 170—180° and the indication is that in this case formation of the amidinium thiocyanate is a more rapid reaction. The low yield of *N*-benzyl-*p*-amidinophenyl methyl sulphone (No. 20) is doubtless due to the rapid and almost complete conversion of benzylammonium thiocyanate into *N*-benzylthiourea (Dixon, *J.*, 1891, **59**, 555). Anilinium thiocyanate is rapidly and almost completely converted into *N*-phenylthiourea above 85° (Krall and Gupta, *J. Indian Chem. Soc.*, 1935, **12**, 629) and only a small yield of N-*phenyl*-p-*amidinophenyl methyl sulphone* is obtained by heating *p*-cyanophenyl methyl sulphone with *N*-phenylthiourea. Moreover, since ammonium thiocyanate and aniline are formed by the decomposition of *N*-phenylthiourea (de Clermont, *Bull. Soc. chim.*, 1876, **25**, 243), it is possible that the *N*-phenylamidine is not produced from the cyanide and the anilinium thiocyanate produced from the *N*-phenylthiourea, but by the interaction of salts of aniline and *p*-amidinophenyl methyl sulphone, produced from ammonium thiocyanate and the cyanide.

p-Methoxyphenyl cyanide affords a 21% yield of *p*-methoxybenzamidine in 4 hours at 180° (No. 4) and if heating is prolonged to 16 hours, *p*-hydroxybenzamidine is obtained in 44% yield. This demethylation is reminiscent of the production of 3-hydroxy-4-methoxyphthalide and methyl cyanide from meconine and potassium cyanide at 180° (Rodinov, Kanevskaja, and Davankov, *Ber.*, 1933, **66**, 1623; *Bull. Soc. chim.*, 1934, **1**, 677). The production of *p*-carbamidobenzamidine from *p*-cyanobenzoic acid and ammonium thiocyanate (No. 5) is not surprising since Kekulé (*Ber.*, 1873, **6**, 113) obtained benzamide from benzoic acid and ammonium thiocyanate at 150—170°. The method fails with 2 : 4-dichlorophenyl cyanide and *o*-cyanophenyl methyl sulphone, so that *o*-substituted amidines are evidently not readily formed by heating an aryl cyanide with ammonium thiocyanate.

The mechanism of the thiocyanate method, which is probably different from that of the ammonium sulphonate method (Part I, *loc. cit.*), is conveniently discussed in a subsequent communication dealing with the action of other ammonium salts and nitrogen compounds upon cyanides.

Experimental.*

The ammonium thiocyanate employed was a commercial sample which was dried at 100° for 1—2 hours before use. The following general description is supplemented by detailed descriptions in those cases where special features are involved. The cyanide and ammonium thiocyanate or substituted ammonium thiocyanate were heated under the conditions specified in the table. If the reactants were immiscible, the mixture was stirred vigorously and heating was continued for *ca.* 1 hour after the two layers had coalesced. The amidine was liberated from an aqueous solution of the product with 5N-sodium

* See also Boots Pure Drug Co. Ltd., Partridge & Short, B.P. Appln. 17,732/11.7.1945.

hydroxide or, in the case of weakly basic amidines, with ammonia, and was separated from unchanged cyanide by solution in hydrochloric acid. The amidine was reprecipitated, washed with ice-water and dissolved in an equivalent of hydrochloric acid. The amidinium chlorides were isolated by concentrating the solutions by distillation under diminished pressure, and the other salts were prepared by double decomposition with sodium picrate, etc.

p-*Carbamidobenzamidine.*—*p*-Cyanobenzoic acid (6 g.) and ammonium thiocyanate (12·2 g.) formed a homogeneous mixture when heated at 180° for 4 mins. with occasional stirring. After 20 mins. a brown solid separated and ammonia was evolved. Heating was continued for a total of 45 mins., and the cold, red melt was boiled with water (30 c.c.) and sufficient hydrochloric acid to give an acid reaction to Congo-red. The solid was extracted with hot water until the extract no longer gave the reaction described by Fuller (*Nature*, 1944, **154**, 773), and the united extracts were warmed to 60° and filtered from *ca.* 2 g. of insoluble material. The filtrate was mixed with excess of saturated aqueous ammonium Reineckate, cooled rapidly, and the Reineckate collected and crystallised from 20% aqueous acetone. The pink needles (7·8 g.) had m. p. 186—188° (decomp.) and afforded the analytical results recorded in the table. The Reineckate (1 g.) was suspended in water (2 c.c.), brought into solution by adding acetone, acidified with a few drops of dilute hydrochloric acid, and shaken with ether (10 c.c.) and acetone (2 drops) until the red colour was removed from the aqueous layer. When excess of saturated aqueous sodium picrate was added to the aqueous solution, *p*-carbamidobenzamidinium picrate, m. p. 274—276°, was precipitated (0·6 g. or 75%) and crystallisation from water produced yellow prismatic needles, m. p. 284—286°. A similar method was used for the conversion of the Reineckate into the hydrochloride (see table).

p-*Amidinophenyl Methyl Sulphone.*—(1) *p*-Cyanophenyl methyl sulphone (9 g.) and ammonium thiocyanate were heated under the conditions shown in the table below. The cold melt was boiled with water (20 c.c.), and the solution poured into a mixture of 10N-sodium hydroxide (15 c.c.) and ice (20 g.), and after being kept at 0° for an hour, the solid was collected, washed with ice-water, and the amidine was extracted from unchanged cyanide (by making an aqueous suspension just acid to brilliant-yellow) with N-hydrochloric acid. The amidine was reprecipitated with 10N-sodium hydroxide (5 c.c.), washed, with ice-water, and determined by titration with standard hydrochloric acid. The amidinium chloride, isolated by concentrating the solution by distillation under diminished pressure, had m. p. 294° in agreement with Fuller *et al.* (*loc. cit.*). The reaction was slightly exothermic and in the experiments at 260° there was vigorous effervescence and evolution of pungent vapours.

NH_4SCN, mols.	Reaction: Temp.	Time, mins.	Yield of amidinium chloride, %.	NH_4SCN, mols.	Reaction: Temp.	Time, mins.	Yield of amidinium chloride, %.
1	260°	30	0·025	4	180°	60	62
1	260	5	28 (*a*)	4	180	45	70
1	150	120	3·4 (*b*)	4	180	30	64
4	225	4	64	4	180	20	37
4	200	30	41	4	170	30	9

(*a*) Recovery of cyanide, 45%. (*b*) Recovery of cyanide, 82%.

(2) A mixture of the cyanide (4·6 g.), ammonium thiocyanate (7·6 g.), and glycerol (20 g.) was heated at 180° for 30 mins. and then boiled with water. The hot filtered solution afforded the amidinium picrate, m. p. 235° (4·7 g.) with alcoholic picric acid. Recrystallisation from alcohol afforded the pure *picrate*, m. p. 262° (Found: N, 16·6. $C_{14}H_{13}O_9N_5S$ requires N, 16·4%). Yield, 3·3 g. (30%). After only 20 minutes at 180° the yield of pure picrate was 2·4 g. (22%).

(3) A mixture of *p*-cyanophenyl methyl sulphone (3·62 g.) and thiourea (6·08 g.; 4 mols.) was heated at 180° for various times with occasional stirring, and an aqueous solution of the resulting yellow gum was decomposed with 5N-sodium hydroxide at 0°. Unchanged cyanide and amidine were separated by extraction with hydrochloric acid, and the amidinium picrate, m. p. and mixed m. p. 263°, was precipitated from the solution with alcoholic picric acid. The yields of amidinium picrate were 22, 51, and 53% after 30, 45, and 60 mins., respectively, at 180°; the corresponding figures when ammonium thiocyanate was used in place of thiourea were 64, 70, and 62%, respectively.

Decomposition of p-*Methylsulphonylbenzamidinium Thiocyanate.*—A hot solution of the amidinium chloride (20 g.) in water (50 c.c.) was mixed with ammonium thiocyanate (6·5 g.; 1 mol.) in water (30 c.c.), shaken with charcoal, filtered, and cooled. The *thiocyanate* (19 g., 88%) separated on cooling in prisms, m. p. 212° (Found: N, 16·4; SCN, 22·5. $C_9H_{11}O_2N_3S_2$ requires N, 16·3; SCN, 22·6%). When the thiocyanate was heated at 225° for 5 mins. the neutral portion of the product consisted of *p*-cyanophenyl methyl sulphone, m. p. and mixed m. p. 142·5° (1·3 g.). The recovered amidinium chloride had m. p. 293° and the amount, determined by titration, was equivalent to 53% of the thiocyanate.

β-Naphthamidine.—(*a*) *β*-Naphthyl cyanide (5 g.) and ammonium thiocyanate (10 g.) were vigorously stirred for an hour at 180° and the cold melt was boiled with water (20 c.c.) and charcoal (0·2 g.) and filtered. The filtrate, mixed with 5N-sodium hydroxide (5 c.c.), was kept at 0° for 30 mins. and the solid was then collected, washed with ice-water, suspended in water (5 c.c.), and rendered acid to Congo-red with hydrochloric acid. Addition of alcoholic picric acid to the solution afforded a picrate, which was collected, washed with a little water and alcohol, and recrystallised from methanol. The *β*-naphthamidinium picrate so obtained (0·25 g., 2·2%) had m. p. and mixed m. p. 247°.

(*b*) Repetition of the experiment with thiourea (10 g.) in place of ammonium thiocyanate afforded 0·05 g. (0·4%) of *β*-naphthamidinium picrate, m. p. and mixed m. p. 247°.

4 : 4′-*Diamidino-αγ-diphenoxypropane.*—The 4 : 4′-dicyano-αγ-diphenoxypropane required for the preparation of this amidine was obtained as follows. *p*-Nitrophenol, alcoholic sodium hydroxide (1 mol.), and trimethylene bromide (0·5 mol.) afforded a 74% yield of 4 : 4′-*dinitro-αγ-diphenoxypropane*, which crystallised from benzene in needles, m. p. 131° (Found: N, 8·9. $C_{15}H_{14}O_6N_2$ requires N, 8·8%).

Amidine.	NH_4SCN or RNH_3SCN, mols.	Reaction. Temp.	Time, mins.	Yield, %.	Amidine salt isolated.	M. p.*	Formula.	Found, N, %.	Required, N, %.
(1) Benzamidine	4	180°	240	50	Picrate	239—240°*	$C_{13}H_{11}O_7N_5$	20·2	20·1
(2) *p*-Bromobenzamidine	4	180	150	63	Picrate	269 *	$C_{13}H_{10}O_7N_5Br$	16·3	16·3
(3) p-*Hydroxybenzamidine*	4	180	120	86	*Hydrochloride*	223—224	$C_7H_9ON_2Cl$	16·3	16·2
(4) *p*-Methoxybenzamidine	4	180	240	21	Picrate	212—213	—	—	—
(5) *p*-Carbamidobenzamidine	4	180	45	39	*Reineckate*	186—188 *	$C_{12}H_{16}ON_6S_4Cr,0·5H_2O$	{25·5 / 25·4}	25·5
(6) *p*-Sulphamidobenzamidine	4	220	4	39	Hydrochloride	246	—	—	—
(7) p-*Amidinophenyl methyl sulphone*	4	180	45	70	Hydrochloride	293	—	—	—
(8) *m*-Amidinophenyl methyl sulphone	4	180	120	84	*Thiocyanate*	184—185	$C_9H_{11}O_2N_3S$	16·2	16·3
(9) *β*-Naphthamidine	4	180	60	2·2	Picrate	247	—	—	—
(10) 4 : 4′-Diamidino-*αγ*-diphenoxypropane	8	180—195	180	61	Hydrochloride	294	$C_{17}H_{22}O_2N_4Cl_2$	14·3	14·5
(11) 4 : 4′-Diamidinodiphenyl ether	7·9	180	360	67	Hydrochloride	305—306	$C_{14}H_{16}ON_4Cl_2,2H_2O$	15·5	15·4
(12) 2-Amidinopyridine	4	180	60	59	Picrate	209	$C_{12}H_{10}O_7N_6$	23·8	24·0
(13) 4 : 4′-Diamidinostilbene	10	180—185	720	70	Hydrochloride	355—360 *	$C_{16}H_{18}N_4Cl_2,2H_2O$	14·9	15·0
(14) *α*-Amidinoheptane	4	180	600	3·5	*Picrate*	170—171	$C_{14}H_{21}O_7N_5$	18·7	18·9
(15) Phenylacetamidine	4	180	360	44	*Picrate*	227—228	$C_{14}H_{13}O_7N_5$	19·1	19·3
(16) *NN*-Dimethylbenzamidine	1	180	150	9·5	*Reineckate*	156—157 *	$C_{13}H_{19}N_6S_4Cr,1·5H_2O$	22·7	22·7
(17) NN-*Pentamethylenebenzamidine*	1	180	180	3·4	*Picrate*	173—174	$C_{18}H_{19}O_7N_5$	16·9	16·8
(18) *N*-Methyl-*p*-amidinophenyl methyl sulphone	1	180	120	45	*Benzenesulphonate*	230—231	$C_{15}H_{16}O_5N_2S_2$	7·7	7·6
(19) *NN*-Dimethyl-*p*-amidinophenyl methyl sulphone	1	180	120	57	Hydrochloride	275 *	$C_{10}H_{15}O_2N_2ClS$	10·45	10·65
(20) *N*-Benzyl-*p*-amidinophenyl methyl sulphone	1	180	120	16	*Reineckate*	192—194 *	$C_{19}H_{23}O_2N_6S_5Cr$	18·6	18·5

* Compounds having m. p.'s marked with an asterisk decompose on melting.

Notes.—Except where otherwise indicated, the experiments were conducted with 0·02—0·05 g.-mol. of cyanide. A thorough examination of the experimental conditions was not made in all cases, so that the yields recorded are not necessarily the highest obtainable.

(1) There was no depression in m. p. on admixture with a specimen of benzamidinium picrate, m. p. 238—239°, prepared as described in Part I (*loc. cit.*).

(2) p-*Bromobenzamidinium thiocyanate* had m. p. 218—219° (Found: N, 16·3; SCN, 22·4. $C_8H_8N_3BrS$ requires N, 16·3; SCN, 22·5%).

(3) *p*-Hydroxybenzamidine was also obtained in 44·5% yield by heating *p*-methoxyphenyl cyanide and ammonium thiocyanate (4 mols.) at 180° for 16·5 hours. It was precipitated from aqueous solutions of its salts by ammonia and separated from water in needles, m. p. 233—234° (decomp.), consisting of a dihydrate after drying over potassium hydroxide in a vacuum (Found: N, 16·4, 16·3; *M*, by titration, 172·5. $C_7H_8ON_2,2H_2O$ requires N, 16·3%; *M*, 172). This phenol is insoluble in aqueous sodium hydroxide and precipitation from its salts with this reagent afforded a substance, m. p. 238—239° (decomp.), shown by analysis to consist of a mixture of amidine and amide. The crude amidine first isolated from the reaction product was sometimes contaminated with guanidine produced from the ammonium thiocyanate. This adsorbed guanidine remained in solution when the mixture of bases was neutralised with benzenesulphonic acid and the solution was cooled at 0° and filtered from *p*-hydroxybenzamidinium benzenesulphonate. Addition of sodium picrate solution to the filtrate afforded guanidine picrate, m. p. 309—310° (decomp.) (Found: N, 29·2. Calc. for $C_7H_8O_7N_6$: N, 29·2%). p-*Hydroxybenzamidinium picrate* crystallised in yellow needles, m. p. 230—231° (decomp.) (Found in material dried at 90°: N, 19·2. $C_{13}H_{11}O_8N_5$ requires N, 19·2%). The *benzenesulphonate* separated from water in needles, m. p. 187° (Found in material dried at 90° for 2 hours: N, 9·7, 9·5. $C_{13}H_{14}O_4N_2S$ requires N, 9·5%). The *sulphate* consisted of prismatic needles, m. p. 290—292° (decomp.) (Found in material dried over sulphuric acid in a vacuum: N, 15·2. $C_7H_8ON_2,\frac{1}{2}H_2SO_4$ requires N, 15·1%); and the *nitrate* crystallised from water in needles, m. p. 265—267° (decomp.) (Found in material dried at 90° for 1 hour: N, 21·1. $C_7H_9O_4N_3$ requires N, 21·1%).

(4) Unchanged *p*-methoxyphenyl cyanide amounted to 61%. The picrate and benzenesulphonate of the amidine did not depress the m. p.'s of authentic specimens prepared as described in Part I (*loc. cit.*).

(5) This compound was obtained from *p*-cyanobenzoic acid. The Reineckate contained SCN, 47·7 ($C_{13}H_{16}ON_6S_4Cr,0·5H_2O$ requires SCN, 47·1%). The *picrate* crystallised from water in prismatic needles, m. p. 283—285° (Found in material dried at 105° for 1 hour: N, 21·4. $C_{14}H_{12}O_8N_6$ requires N, 21·4%). The hydrochloride had m. p. 304—305° (decomp.) (Found in material dried at 90° for 1 hour: N, 20·7. Calc. for $C_8H_9O_2N,HCl$: N, 21·0%); Andrewes, King, and Walker (*Proc. Roy. Soc.*, 1946, *B*, **133**, 20) state that the monohydrate has m. p. 302—303°.

(6) The m. p. was undepressed on admixture with an authentic specimen of *p*-sulphamidobenzamidinium chloride prepared as described in Part I (*loc. cit.*).

(7) See below for additional data.

(8) Fuller, Tonkin, and Walker (*J.*, 1945, 633) prepared this amidine by the Pinner method and state that the hydrochloride has m. p. 216°.

(9) The amidine was also prepared from β-naphthyl cyanide and thiourea (see below), and the picrate from the base did not depress the m. p. of authentic β-naphthamidinium picrate.

(10) After 1 hour at 190—195°, heating was continued for 2 hours at 180°. The amidinium chloride sintered at *ca.* 135° before melting at 294°; it was dried at 100° for 2 hours in a vacuum before analysis. The free base had m. p. 190—191° (decomp.). May and Baker, Ashley, Barber, Ewins, Newbery and Self (B.P. 507,565; see *J.*, 1942, 110) state that the free base and hydrochloride monohydrate have m. p. 193—194° (decomp.) and 292°, respectively.

(11) Preparation by Dr. A. Koebner (Found in the hydrochloride: Cl, 19·5. H_2O, 10·2. Calc.: Cl, 19·6; H_2O, 9·9%). This amidine was prepared from 0·1 g.-mol. of 4:4′-dicyanodiphenyl ether. The free base had m. p. 215—216° in agreement with May and Baker, Ashley *et al.* (*loc. cit.*).

(12) The picrate did not depress the m. p. of a sample prepared as described in Part I (*loc. cit.*).

(13) Preparation by Mr. S. W. Stroud using 0·22 g.-mol. of crude 4:4′-dicyanostilbene [Found in the dihydrochloride dihydrate: Cl, 18·85; H_2O (at 100°), 9·4. Calc.: Cl, 19·0; H_2O, 9·65%]. May and Baker, Ashley *et al.* (B.P. 510,097; and *J.*, 1942, 110) state that the dihydrochloride dihydrate has m. p. 300°.

(14) Found in the picrate: C, 45·3; H, 5·3. $C_{14}H_{21}O_7N_5$ requires C, 45·5; H, 5·7%.

(15) Phenylacetamidine has been described by Bernthsen (*Annalen*, 1877, **184**, 321, 340) and by Luckenbach (*Ber.*, 1884, **17**, 1423).

(16) Found in the Reineckate: SCN, 47·1, 46·8. $C_{19}H_{19}N_8S_4Cr,1·5H_2O$, requires SCN, 47·0%. Phenyl cyanide (79%) was recovered.

(17) The recovery of phenyl cyanide was 90%. The isolation of this amidine is described in the experimental section.

(18) The amidinium chloride has been prepared by the Pinner method (Fuller, Tonkin, and Walker, *loc. cit.*).

(19) The m. p. of the hydrochloride agrees with that recorded by Fuller *et al.* (*loc. cit.*). The *picrate* crystallised from methanol in short needles, m. p. 189·5° (Found: N, 15·4. $C_{14}H_{17}O_8N_5S$ requires N, 15·4%).

(20) The benzenesulphonate was obtained as an oil.

Reduction of the dinitro-compound with aqueous sodium sulphide gave an 88% yield of 4 : 4′-*diamino-αγ-diphenoxypropane*, m. p. 108—109° (Found : N, 10·8. $C_{15}H_{16}O_2N_2$ requires N, 10·85%), and the portion of the product insoluble in dilute hydrochloric acid consisted essentially of 4-*nitro*-4′-*amino-αγ-diphenoxypropane*, which crystallised from aqueous alcohol in yellow leaflets, m. p. 124—125° (Found : N, 9·7. $C_{15}H_{16}O_4N_2$ requires N, 9·7%). The yield of nitroamine was 11%, and 0·6% of the dinitro-compound was recovered. A 54% yield of 4 : 4′-dicyano-αγ-diphenoxypropane, m. p. 182—184°, was obtained by the Sandmeyer reaction, and recrystallisation from ethyl acetate raised the m. p. to 186—187°. Ashley *et al.* (*loc. cit.*, p. 114) record m. p. 188°.

A mixture of the dicyanide (5·6 g.) and ammonium thiocyanate (12·2 g.) was heated and stirred under the conditions specified in the table and the amidine was isolated from the melt in the usual way.

NN-*Pentamethylenebenzamidine*.—Phenyl cyanide (5·2 g.) and piperidinium thiocyanate (7·2 g.; Gebhardt, *Ber.*, 1884, **17**, 3041; Hofmann and Gabriel, *Ber.*, 1892, **25**, 339) afforded a homogeneous brown melt when heated at 180° for 3 hours with occasional stirring. The product was stirred with 5N-sodium hydroxide (20 c.c.) and extracted with chloroform (5 × 50 c.c.). The amidine was extracted from the concentrated chloroform solution with dilute hydrochloric acid, and phenyl cyanide, b. p. 185—190° (4·7 g.), was recovered after removal of the solvent. The aqueous solution was made alkaline with 10N-sodium hydroxide and extracted with chloroform. The solvent was removed from the dried solution, and distillation of the residue afforded NN-*pentamethylenebenzamidine*, b. p. 104°/0·6 mm. (Found : N, 14·9. $C_{12}H_{16}N_2$ requires N, 14·9%). The picrate was prepared by adding aqueous sodium picrate to a solution of the amidinium chloride (see table).

N-*Methyl*-p-*amidinophenyl Methyl Sulphone*.—Hot solutions of methylammonium chloride (67·5 g.) in 95% alcohol (300 c.c.) and ammonium thiocyanate (76 g.; 1 mol.) in 95% alcohol (200 c.c.) were mixed, cooled rapidly, and filtered from ammonium chloride. The filtrate was evaporated below 40°, and the residue dried over sulphuric acid in a vacuum and extracted with hot absolute alcohol (200 c.c.), leaving ammonium chloride undissolved. When the filtrate was cooled to 0° part of the thiocyanate was deposited and the rest was obtained by concentrating the filtrate below 40°. After drying in a vacuum over sulphuric acid the *methylammonium thiocyanate* (85 g.) was obtained in deliquescent crystals, m. p. 73—74° (Found : N, 30·7; SCN, 64·5. $C_3H_6N_2S$ requires N, 31·1; SCN, 64·5%). *p*-Cyanophenyl methyl sulphone (9 g.) and methylammonium thiocyanate (4·5 g.) were heated under the conditions specified in the table and a suspension of the product in water (15 c.c.) was poured into 10N-sodium hydroxide (25 c.c.) and ice (25 g.). The solid was collected after 2 hours at 0° and the filtrate (A) was kept. When the solid was extracted with dilute hydrochloric acid, unchanged cyanide, m. p. 140—141° (4·24 g.), remained undissolved, and the base, precipitated from the aqueous solution by adding alkali, was collected and the filtrate added to the solution A. The solid was suspended in water, neutralised to brilliant-yellow with aqueous benzenesulphonic acid, and evaporated to dryness, giving 6·2 g. of the benzenesulphonate, m. p. 230—231°. Amidine remaining in the alkaline aqueous solutions (A) was recovered by extraction with chloroform and converted into the benzenesulphonate, m. p. 229—230° (2·1 g.). Recrystallisation from water afforded prisms of the pure benzenesulphonate, m. p. 230—231° (see table).

N-*Phenyl*-p-*amidinophenyl Methyl Sulphone*.—*p*-Amidinophenyl methyl sulphone (9 g.) and *N*-phenylthiourea (7·6 g.; 1 mol.) were heated at 155° with stirring for 30 hours. The product was extracted with boiling acetone (100 c.c.), and the solution concentrated to 20 c.c., mixed with 5N-sodium hydroxide (20 c.c.) and repeatedly extracted with chloroform (280 c.c. in all). The solvent was removed and the residue extracted with warm dilute hydrochloric acid, leaving a resin undissolved. The acid solution was mixed with ammonia (*d* 0·88; 20 c.c.), cooled to 0°, and filtered. Addition of 5N-sodium hydroxide (5 c.c.) to the filtrate afforded p-*amidinophenyl methyl sulphone* (0·07 g.), m. p. 200—202° (decomp.) (Found : N, 13·9. $C_8H_{10}O_2N_2S$ requires N, 14·1%). The first precipitate afforded a gummy benzenesulphonate (2·8 g.) when its solution in an equivalent of aqueous benzenesulphonic acid was evaporated to dryness. The gum was dissolved in water, the solution made alkaline with ammonia, and the solid collected and recrystallised from alcohol (charcoal), giving *N*-phenyl-*p*-amidinophenyl methyl sulphone (0·4 g.), m. p. and mixed m. p. 230—231°.

We are indebted to Mr. P. Oxley for an authentic specimen of N-*phenyl*-p-*amidinophenyl methyl sulphone*, which crystallised from methanol in needles, m. p. 231° (Found : N, 10·4, 10·4. $C_{14}H_{14}O_2N_2S$ requires N, 10·2%). By heating a mixture of *p*-cyanophenyl methyl sulphone (9·05 g.) and anilinium benzenesulphonate (12·55 g.; 1·0 mol.) at 175—180° for 3 hours, he obtained an 86·5% yield of N-*phenyl*-p-*methylsulphonylbenzamidinium benzenesulphonate*, m. p. 222° (Found : N, 6·6. $C_{20}H_{20}O_6N_2S_2$ requires N, 6·5%).

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[*Received, June 27th*, 1946.

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79. *Amidines. Part V. Preparation of Amidines from Cyanides and Substituted Aminomagnesium Halides.*

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Amidines are formed by decomposition of the complexes produced from alkyl or aryl cyanides and aminomagnesium halides, NRR′·MgHal. When R = R′ = H, the yields are very small, and no reaction occurs when R = R′ = Ar. The reaction also fails with benzyl cyanide which is converted into a dimeride.

Oddo and Calderaro (*Gazzetta*, 1923, **53**, 64) state that phenyl cyanide and aminomagnesium bromide combine in presence of ether to give an addition compound from which the cyanide is regenerated by the action of water. We find that, in anisole, phenyl cyanide and aminomagnesium iodide afford a small yield of benzamidine and that moderately good yields of substituted amidines may be obtained by the interaction between alkyl or aryl cyanides and diethylaminomagnesium bromide, benzylaminomagnesium bromide, methylanilinomagnesium bromide, or anilinomagnesium bromide in ethereal solution :

$$R{\cdot}CN + NR'R''{\cdot}MgBr \longrightarrow R{\cdot}C(:NMgBr){\cdot}NR'R'' \longrightarrow R{\cdot}C(:NH){\cdot}NR'R''$$

No amidine could be obtained from diphenylaminomagnesium bromide and either phenyl cyanide or *p*-cyanophenyl methyl sulphone even in anisole at 100°. Benzyl cyanide is largely converted into β-imino-α-cyano-αγ-diphenylpropane by either diethylaminomagnesium bromide or methylanilinomagnesium bromide and no amidine is formed. This dimeride was isolated by Rondou (*Bull. Soc. chim. Belg.*, 1922, **31**, 239) from the mixture obtained from benzyl cyanide and methylmagnesium bromide and is probably formed by addition of benzyl cyanide to its magnesium derivative :

$$Ph{\cdot}CH_2{\cdot}CN + Ph{\cdot}CH{:}C{:}NMgBr \longrightarrow Ph{\cdot}CH_2{\cdot}C(:NMgBr){\cdot}CHPh{\cdot}CN \longrightarrow Ph{\cdot}CH_2{\cdot}C(:NH){\cdot}CHPh{\cdot}CN$$

Diethylcyanamide and diethylaminomagnesium bromide afford *s*-tetraethylguanidine in 58% yield.

Experimental.*

Benzamidine.—Ethylmagnesium iodide (from ethyl iodide, 31·2 g.; magnesium, 4·8 g.; and ether 60 c.c.) was added to a 0·4N-solution of ammonia in ether (500 c.c.). When the evolution of ethane had ceased, anisole (100 c.c.) was added, and the ether was removed from the suspension of aminomagnesium iodide by distillation. After addition of phenyl cyanide (20·6 g.), the mixture was stirred at room temperature for 48 hours and then poured into 5N-hydrochloric acid (100 c.c.) and ice (300 g.). The aqueous solution was extracted with ether, and phenyl cyanide (12 g.) was recovered from the united ethereal and anisole solutions. The acid solution was made alkaline with 5N-sodium hydroxide (200 c.c.), and the precipitated magnesium hydroxide was removed, washed with chloroform, and the solution added to a chloroform extract of the filtrate. The residue obtained by evaporating the chloroform solution afforded benzamidinium picrate (1·2 g.), m. p. and mixed m. p. 239—241°, with alcoholic picric acid.

N-*Benzylbenzamidine.*—A solution of benzylamine (21·4 g.) in ether (60 c.c.) was added to ethylmagnesium bromide (from ethyl bromide, 24·2 g.; magnesium, 4·8 g.; and ether, 90 c.c.) and, after boiling for 10 minutes, the mixture was cooled. An exothermic reaction occurred when a solution of phenyl cyanide (20·6 g.) in dry ether (60 c.c.) was added, and an oil separated. The mixture was stirred with ice and hydrochloric acid, and the benzylbenzamidinium chloride, m. p. 227—229°, which separated was collected. Pyman (*J.*, 1923, **123**, 3373) records m. p. 227—229° (corr.). The filtrate was made alkaline, filtered from magnesium hydroxide, and extracted with chloroform. Distillation of the chloroform extract (14 g.) afforded benzylamine, b. p. 66—68°/1 mm. (4 g.), and a semi-solid residue of amidine (10 g. or 24%) which gave a picrate, m. p. 169—170° (Found : N, 15·85. Calc. for $C_{20}H_{17}O_7N_5$: N, 15·9%). Pyman (*loc. cit.*) states that *N*-benzylbenzamidine has m. p. 77—78° and affords a picrate, m. p. 169—170°.

NN-*Diethyl*-n-*valeramidine.*—A solution of diethylamine (14·6 g.) in dry ether (50 c.c.) was added with stirring to ethylmagnesium bromide (from ethyl bromide, 24·2 g.; magnesium 4·6 g.; and ether, 90 c.c.) and the mixture was boiled until no more ethane was evolved. A solution of *n*-butyl cyanide (16·6 g.) in ether (60 c.c.) was added, and the mixture was boiled for 30 mins., cooled, and poured with stirring into saturated ethereal hydrogen chloride (200 c.c.). Cold water was then added and the aqueous solution was removed, cooled in ice, and made alkaline with 5N-sodium hydroxide. The magnesium hydroxide was washed with chloroform and the filtrate was extracted with the same solvent. The chloroform solution afforded *NN*-diethyl-*n*-valeramidine, b. p. 60°/1 mm. (8 g. or 26%), which was characterised as the *picrate*, m. p. 93° (Found : N, 17·8. $C_{15}H_{23}O_7N_5$ requires N, 18·2%).

NN-*Diethylbenzamidine.*—This amidine, b. p. 95°/2 mm., was prepared in 58% yield in the same way from phenyl cyanide and diethylaminomagnesium bromide in dry ether. The picrate, m. p. 161°, did not depress the m. p. of an authentic specimen prepared by Mr. P. Oxley by a different method.

N-*Phenyl*-N *methylbenzamidine.*—Methylanilinomagnesium iodide was prepared by adding methylaniline (21·4 g.) in ether (60 c.c.) to an ethereal solution of ethylmagnesium iodide (1 mol.) and boiling for 15 mins. to complete the reaction. A solution of phenyl cyanide (20·6 g.) in ether (60 c.c.) was then added slowly, with subsequent stirring at room temperature for 2 hrs. The complex was decomposed in the usual way, and the amidine collected in chloroform and crystallised from light petroleum. The *N*-phenyl-*N*-methylbenzamidine (11·5 g. or 25%) so obtained had m. p. 85° (Found : N, 13·2. Calc. for $C_{14}H_{14}N_2$: N, 13·3%) in agreement with v. Pechmann (*Ber.*, 1897, **30**, 1782). The picrate had m. p. 186—188° (Found : N, 15·7. Calc. for $C_{20}H_{17}O_7N_5$: N, 15·9%); v. Pechmann (*loc. cit.*) records m. p. 184°.

N-*Phenyl*-p-*methoxybenzamidine.*—A solution of *p*-methoxyphenyl cyanide (13·5 g.) in ether (150 c.c.) was slowly added at room temperature to anilinomagnesium bromide, prepared in the usual way from ethyl bromide (10·9 g.), magnesium (2·3 g.), aniline (9·3 g.), and ether (90 c.c.). After being stirred

* See also B.P. Appln. 23,412/11·9·1945.

for 2 hrs., the mixture was added to 5N-hydrochloric acid (50 c.c.) and ice (150 g.), and the solid was crystallised from acetone–alcohol, giving N-*phenyl*-p-*methoxybenzamidinium chloride*, m. p. 224—225° (Found: N, 10·7. $C_{14}H_{15}O_2N_2Cl$ requires N, 10·7%). The yield was 25%, and 8·4 g. of the cyanide were recovered from the ethereal solution. N-*Phenyl*-p-*methoxybenzamidine*, liberated from the chloride by cold aqueous sodium hydroxide, crystallised from *iso*propanol in plates, m. p. 147—149° (Found: N, 12·6. $C_{14}H_{14}O_2N_2$ requires N, 12·4%).

s-*Tetraethylguanidine*.—Diethylaminomagnesium bromide was prepared from diethylamine (10·3 g.) in the usual way, a solution of diethylcyanamide (9·8 g.; McKee, *Amer. Chem. J.*, 1906, **36**, 210) in ether (100 c.c.) was added with cooling, and stirring was continued for ¾ hr. The mixture of ether and thin oil was decomposed with ice and concentrated hydrochloric acid (20 c.c.), and the aqueous layer was extracted with ether and made alkaline to Titan-yellow with 5N-sodium hydroxide. Magnesium hydroxide was removed and the filtrate shaken with chloroform (2 × 100 c.c.) which extracted s-tetraethylguanidine, b. p. 71°/2 mm. (10 g., 58%). Lecher and Demmler (*Z. physiol. Chem.*, 1927, **167**, 175) state that s-tetraethylguanidine has b. p. 83·5°/10 mm. The *picrate*, m. p. 85°, was prepared from the base and alcoholic picric acid (Found: N, 20·8. $C_{15}H_{24}O_7N_6$ requires N, 21·0%). Lecher and Demmler (*loc. cit.*) obtained an oily picrate.

β-*Imino*-α-*cyano*-αγ-*diphenylpropane*.—Methylanilinomagnesium bromide and benzyl cyanide (1 mol.) were brought into reaction in ether and the product was decomposed with cold dilute acid in the usual way. The ethereal solution contained unchanged benzyl cyanide, b. p. 62°/2 mm. (13%), and a viscous oil, b. p. 206°/1 mm. (81%), which set to a resin on cooling (Found: N, 11·8. Calc. for C_8H_7N: N, 11·9%). The b. p. of this product agrees with that of the dimeride of benzyl cyanide obtained by Meyer (*J. pr. Chem.*, 1895, **52**, 114; 1908, **78**, 497) and shown by Atkinson and Thorpe (*J.*, 1906, **89**, 1934) and Lees and Thorpe (*J.*, 1907, **91**, 1287) to be β-imino-α-cyano-αγ-diphenylpropane. Rondou (*loc. cit.*) obtained this dimeride in solid form, m. p. 114·5—115°. Similarly, benzyl cyanide and diethylaminomagnesium bromide afforded 75% of the dimeride and 21% of recovered cyanide.

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[*Received, June 28th*, 1946.]

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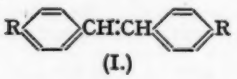
80. *The Conversion of Sucrose into Furan Compounds. Part III. Some Amidino-furans.*

By F. H. NEWTH and L. F. WIGGINS.

Several new amidino-derivatives of furan have been obtained. Two of them, namely 5 : 5′-diamidino-αβ-2 : 2′-difurylethane and 5 : 5′-*diamidinodifurfuryl ether*, are analogues of diamidines of the benzene series found to be active against trypanosomes. The new furan compounds, however, possess high toxicity and show only little activity against *T. equiperdum in vivo*.

SINCE it was demonstrated (Warrington Yorke *et al.*, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1940, **33**, 463) that certain amidine derivatives possessed trypanocidal activity, the value of this type of drug in combating trypanosomiasis and leischmaniasis has been well established. Subsequently a great deal of effort has been directed towards the preparation and chemotherapeutic evaluation of a large number of amidino-compounds. Ewins *et al.* (*J.*, 1942, 103), have found that the most active compounds in the benzene series are " stilbamidine " [4 : 4′-diamidinostilbene (I)], 4 : 4′-diamidino-αγ-diphenoxypropane, 4 : 4′-diamidino-αε-diphenoxypentane, 4 : 4′-diamidinodibenzyl ether (II), and 4 : 4′-diamidino-αβ-diphenylethane (III).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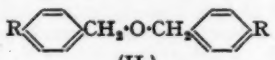
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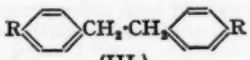
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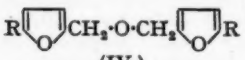
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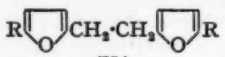
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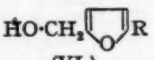
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[R = C(:NH)·NH$_2$.]

It occurred to us that it would be of interest to prepare the furan analogues of some of these compounds in order to discover the effect on trypanocidal activity of replacement of the benzene by the furan nucleus. Furan analogues of compounds (II) and (III), namely 5 : 5′-*diamidinodifurfuryl ether* (IV) and 5 : 5′-diamidino-αβ-2 : 2′-difurylethane (V) (isolated at its *dihydrochloride*), have now been obtained. Only the latter, however, showed any trypanocidal activity. A mono-amidino-compound, 5-amidinofurfuryl alcohol (VI) (isolated as its *hydrochloride*) was also prepared, but this possessed no activity against trypanosomes.

Compound.	Minimum effective dose (mg./g.).	Maximum tolerated dose (mg./g.).
4 : 4′-Diamidinodibenzyl ether	0·0005	0·015
4 : 4′-Diamidino-αβ-diphenylethane	0·001	0·015
5 : 5′-Diamidino-αβ-2 : 2′-difurylethane	0·025	0·25
5 : 5′-Diamidinodifurfuryl ether	No action	0·25
5-Amidinofurfuryl alcohol	No action	2·5

The new amidinofurans were obtained in the following way. A convenient starting material for the synthesis of 5 : 5′-diamidinodifurfuryl ether was 5 : 5′-diformyldifurfuryl ether, a by-product in the preparation of 5-hydroxymethylfurfuraldehyde by the action of oxalic acid on sucrose (Kiermayer, *Chem. Ztg.*, 1895, **19**, 1003; Haworth and Jones, *J.*, 1944, 667). The dialdehyde was converted into its dioxime and this, by dehydration with acetic anhydride, gave *5 : 5′-dicyanodifurfuryl ether* which was then converted into its *di-iminoether dihydrochloride*. The conversion of this substance into the diamidine proved somewhat difficult. The iminoether possessed considerable stability towards ammonia at 0°, the usual procedure for conversion of an iminoether into an amidine, and by this treatment the dihydrochloride gave only the free iminoether, identified as its dihydrochloride, and ammonium chloride. To form the amidino-compound it was necessary to employ alcoholic ammonia at 100° under pressure, and under these conditions 5 : 5′-diamidinodifurfuryl ether was obtained, and was further characterised as its *dipicrate*.

5 : 5′-Diamidino-αβ-2 : 2′-difurylethane was synthesised from the main product of the action of dilute oxalic acid on sucrose, namely 5-hydroxymethylfurfuraldehyde. This was converted by a modified procedure of Middendorp (*Rec. Trav. chim.*, 1919, **38**, 1) into 5-bromomethylfurfuraldehyde which, on treatment with freshly precipitated silver according to the method of Fenton and Gostling (*J.*, 1901, **79**, 807), gave αβ-2 : 2′-difurylethane-5 : 5′-dialdehyde. The dioxime of this compound gave *5 : 5′-dicyano-αβ-2 : 2′-difurylethane* on dehydration. The *di-iminoether dihydrochloride* obtained therefrom proved to be just as stable to ammonia as the corresponding derivative of 5 : 5′-diformyldifurfuryl ether, and its treatment with ammonia in the cold led mainly to the formation of the free *di-iminoether*, together with ammonium chloride and a very small amount of 5 : 5′-diamidino-αβ-2 : 2′-difurylethane. The purification of the free di-iminoether was achieved with some difficulty, although its dihydrochloride was a well-defined compound. When the difurylethanedi-iminoether dihydrochloride was treated with alcoholic ammonia at 110°, the diamidine was the main product.

5-Amidinofurfuryl alcohol was obtained from 5-hydroxymethylfurfuraldehyde by the usual procedure.

Experimental.

Dioxime of 5 : 5′-Diformyldifurfuryl Ether.—5 : 5′-Diformyldifurfuryl ether (7·2 g.), obtained as a by-product in the preparation of 5-hydroxymethylfurfuraldehyde from sucrose, was dissolved in 50% alcohol (130 c.c.), and a solution containing hydroxylamine hydrochloride (8·6 g.) and sodium carbonate (6·5 g.) in water (50 c.c.) added. The solution was boiled under reflux for 3 hours and, on cooling, crystalline material separated. This recrystallised from alcohol in the form of fine needles, m. p. 167—168° (Kiermayer, *loc. cit.*, gives m. p. 167°). Yield, 1·25 g. (Found : C, 54·8; H, 4·6. Calc. for $C_{12}H_{12}O_5N_2$: C, 54·8; H, 4·6%).

5 : 5′-Dicyanodifurfuryl Ether.—The dioxime (1·25 g.) was boiled under reflux with acetic anhydride (50 c.c.) for 1 hour. Thereafter it was poured into water and neutralised with sodium bicarbonate, and the solution extracted thrice with chloroform. The combined extracts were dried ($MgSO_4$) and filtered with charcoal. Evaporation of the solvent under diminished pressure gave a syrup which crystallised on trituration with alcohol; on recrystallisation from alcohol–water the *dicyanide* formed pale yellow plates, m. p. 57—58°. Yield, 0·78 g. (Found : C, 63·5; H, 3·3; N, 12·8. $C_{12}H_8O_3N_2$ requires C, 63·2; H, 3·5; N, 12·3%).

Difurfuryl Ether 5 : 5′-Di-iminoether Dihydrochloride.—The dicyanide (3·4 g.) was dissolved in absolute alcohol (40 c.c.) saturated with dry hydrogen chloride at 0°, and the solution kept thereat for 48 hours. The crystalline material which separated was filtered off and washed with dry ether until free from hydrogen chloride. Yield, 5·5 g. (96%). Recrystallised from absolute alcohol, the *dihydrochloride* had m. p. 134—135° (decomp.) (Found : C, 48·7; H, 5·2; N, 7·3. $C_{16}H_{20}O_5N_2,2HCl$ requires C, 48·8; H, 5·6; N, 7·1%).

The iminoether (5 g.) was treated with absolute alcoholic ammonia (saturated at 0°) and the solution kept at 0° for 48 hours. Thereafter, evaporation to a quarter volume led to the separation of ammonium chloride (0·3 g.). Further evaporation of the solvent gave a syrup (3·9 g.), which was alkaline to litmus. On passing dry hydrogen chloride into an ethereal solution of the syrup the dihydrochloride of the iminoether was recovered, m. p. 133—135°.

5 : 5′-Diamidinodifurfuryl Ether.—The iminoether hydrochloride (2·4 g.) was heated at 110° for 8 hours with absolute alcoholic ammonia (100 c.c. saturated at 0°). On cooling, crystals separated which, when recrystallised from absolute alcohol, formed plates, m. p. 198—198·5° (1·07 g.) (Found : C, 54·7; H, 5·3. $C_{12}H_{14}O_3N_4$ requires C, 54·7; H, 5·3%). The *amidine* was only sparingly soluble in water

(0·2 g./100 g. H_2O). The *dipicrate* recrystallised from water in the form of plates and had an indefinite decomposition point above 300° (Found: C, 40·3; H, 3·1. $C_{24}H_{20}O_{17}N_{10}$ requires C, 40·0; H, 2·8%).

5-Bromomethylfurfuraldehyde.—5-Hydroxymethylfurfuraldehyde (50 g.) dissolved in dry ether (200 c.c.) was added slowly to a solution of dry hydrogen bromide in dry ether (50%) at 0°. The mixture was allowed to reach room temperature and kept thereat for 2 hours. By this time signs of humin formation had become apparent and the solution was dark purple. It was neutralised with anhydrous sodium carbonate, the ethereal solution filtered, and the solid residue washed thoroughly with ether. Evaporation of the combined filtrate and washings gave a syrup (47 g.) which crystallised completely on nucleation. Recrystallisation from ether gave 5-bromomethylfurfuraldehyde, m. p. 59—60°, in yellow prisms (40% yield). The procedure is a modification of that of Middendorp (*loc. cit.*).

αβ-2 : 2′-Difurylethane-5 : 5′-dialdehyde.—5-Bromomethylfurfuraldehyde (13·8 g.) was dissolved in dry benzene (25 c.c.) and finely divided silver (30 g.) added. After boiling under reflux for 6 hours, the silver residues were extracted with boiling benzene several times and the combined extracts evaporated. The semi-solid mass was washed with a little benzene so that a yellow crystalline material (7·7 g.) remained. This recrystallised from benzene in yellow needles, m. p. 118—120° (Fenton and Gostling, *loc. cit.*, give m. p. 119·5—121°). Evaporation of the benzene washings gave a little more material. Total yield, 4·5 g. (54·5%).

αβ-2 : 2′-Difurylethane-5 : 5′-dialdoxime.—This was prepared according to the procedure of Fenton and Gostling (*loc. cit.*) but it had m. p. 200·5—201·5° whereas the earlier workers record m. p. 182° (Found: C, 58·4; H, 4·8; N, 11·8. Calc. for $C_{12}H_{12}O_4N_2$: C, 58·1; H, 4·8; N, 11·3%).

5 : 5′-Dicyano-αβ-2 : 2′-difurylethane.—Difurylethanedialdoxime (1·77 g.) was boiled under reflux with acetic anhydride (25 c.c.) for ½ hour. The solution was poured into water, neutralised with sodium bicarbonate, and extracted with chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and evaporated to dryness. The *dicyanide* recrystallised from alcohol in pale yellow needles, m. p. 115—116° (Found: C, 68·4; H, 3·6; N, 13·0. $C_{12}H_8O_2N_2$ requires C, 67·9; H, 3·7; N, 13·2%).

αβ-2 : 2′-Difurylethane-5 : 5′-di-iminoether Dihydrochloride.—The above dicyanide (2·4 g.) was treated with absolute alcohol saturated with dry hydrogen chloride at 0° (150 c.c.) for 4 days. The crystals which had separated were filtered off and washed with dry ether until free from hydrogen chloride. Yield, 2·5 g.; m. p. 245—252°. After recrystallisation from absolute alcohol, the *dihydrochloride* had m. p. 253—255° (Found: N, 7·2. $C_{10}H_{20}O_4N_2,2HCl$ requires N, 7·4%).

The iminoether dihydrochloride (4·0 g.) was treated with a solution of alcoholic ammonia (100 c.c. saturated at 0°) for 2 days. On evaporation of the solution to half volume crystals of ammonium chloride (0·9 g.) separated. Further evaporation gave a solid residue. This was extracted with ether, and from the ethereal extract upon cooling there were deposited feathery crystals of *αβ-2 : 2′-difurylethane 5 : 5′-di-iminoether*, m. p. 79—80·5° (Found: N, 8·8. $C_{10}H_{20}O_4N_2$ requires N, 9·2%). The ether-insoluble residue was dissolved in alcohol, and a little ether added, when unchanged dihydrochloride was isolated. Further addition of ether gave more of the free base contaminated with ammonium chloride.

5 : 5′-Diamidino-αβ-2 : 2′-difurylethane Dihydrochloride Dihydrate.—The iminoether dihydrochloride (2·6 g.) was heated with ethyl alcoholic ammonia (100 c.c.) at 110° for 6 hours. On evaporation to 20 c.c., fine needles (1·04 g.) separated which, on being recrystallised from ethyl alcohol, had m. p. 251° (Found: C, 40·3; H, 5·6; N, 15·5; H_2O, 10·6. $C_{12}H_{14}O_2N_4,2HCl,2H_2O$ requires C, 40·5; H, 5·6; N, 15·8; H_2O, 10·2%). This *dihydrate* of 5 : 5′-diamidinodifurylethane dihydrochloride was soluble in water to the extent of 2·7 g. per 100 c.c. of solution. On being heated at 110° for 3 hours, it yielded the anhydrous *salt*, m. p. 282—283° (Found: C, 45·8; H, 5·2. $C_{12}H_{14}O_2N_4,2HCl$ requires C, 45·1; H, 5·0%).

2-Cyano-5-acetoxymethylfuran.—5-Hydroxymethylfurfuraldoxime (Kiermayer, *loc. cit.*) (21 g.) was boiled under reflux with acetic anhydride (60 c.c.) and fused sodium acetate (3 g.) for ½ hour. After being poured into water, the solution was neutralised with sodium bicarbonate and then extracted with ether. The extract was dried ($MgSO_4$), the solution filtered, and the ether removed. The liquid remaining distilled at 140° (bath temp.)/0·01 mm. as a colourless oil having $n_D^{16°}$ 1·4970. Yield, 16·4 g. (Found: N, 8·9. $C_8H_7O_3N$ requires N, 8·5%).

5-Acetoxymethylfuran-2-iminoether Hydrochloride.—The above *cyanide* (7·5 g.) was dissolved in absolute alcohol (20 c.c.) saturated with dry hydrogen chloride, and kept at 0° for 4 days. The iminoether *hydrochloride* which separated was filtered off and washed with dry ether until free from hydrogen chloride. It recrystallised from absolute alcohol–ether in clusters of needles, m. p. 121—121·5° (6·6 g.) (Found: C, 48·2; H, 5·9. $C_{10}H_{13}O_4N,HCl$ requires C, 48·4; H, 6·1%).

5-Amidinofurfuryl Alcohol Hydrochloride.—The iminoether hydrochloride (5 g.) was dissolved in absolute alcohol saturated with ammonia at 0° and kept at 0° for 24 hours. On evaporation of the solvent at room temperature under diminished pressure a solid residue was obtained which recrystallised from dry alcohol–ether in needles, m. p. 147—148°. It was very soluble in water (Found: C, 40·7; H, 5·1; N, 15·5. $C_6H_9O_2N_3,HCl$ requires C, 40·9; H, 5·1; N, 15·9%). The same *product* was obtained if the reaction was conducted at 110° in a sealed tube. The amidine formed a well-defined *picrate* which recrystallised from water in needles, m. p. 223—225° (Found: C, 39·0; H, 3·1. $C_{12}H_{11}O_9N_5$ requires C, 39·1; H, 3·0%).

The authors are grateful to Professor C. R. Harington, F.R.S., Director of Research, Medical Research Council, who arranged for the testing of the compounds for trypanocidal activity. Their thanks are also due to the Colonial Products Research Council for financial support.

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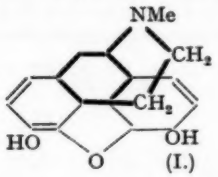
[*Received, June 18th*, 1946.]

81. *Syntheses in the Morphine Series. Part I. Derivatives of* bicyclo[3 : 3 : 1]-2-*Azanonane.*

By J. A. Barltrop.

The synthesis of certain bi- and tri-cyclic ring-systems occurring in the morphine molecule has been effected by cyclisation of the β-diethylaminoethyl derivatives of ethyl *cyclo*hexanone-carboxylate and of 1-alkyl-β-tetralones to the corresponding *bicyclo*[3 : 3 : 1]-2-azanonanes.

This paper is the first of a series embodying the results of preliminary experiments directed toward the synthesis of members of the morphine sub-group of alkaloids. Previous work in this field has been executed largely by Robinson *et al.* (*J.*, 1931, 3163, 3173; 1932, 785, 789), Robinson and Ghosh (*J.*, 1944, 506), Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1104), Fieser and Holmes (*ibid.*, 1938, **60**, 2548), Koelsch (*ibid.*, 1945, **67**, 569), Holmes and Trevoy (*Canad. J. Res.*, 1944, *B*, **22**, 56, 109), and Grewe (*Ber.*, 1939, **72**, 426, 785, 1314; 1943, **76**, 1072, 1076). There are two possible approaches to the problem of the synthesis of morphine; first by a step-by-step synthesis in the classical tradition, and secondly by methods depending on theories as to the probable course of the phytochemical synthesis. Researches are being pursued along both channels, but herein are reported only the results of investigations along the first. Examination of the Gulland and Robinson structure of the morphine molecule suggests that one of the most difficult stages is likely to be the formation of the nitrogen-containing *meta*-bridged system (I, heavy lines), and this paper describes the synthesis of such a system in model substances.



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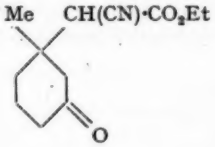

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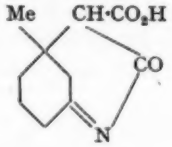
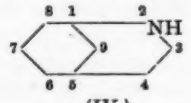
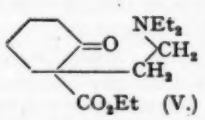


(III.)

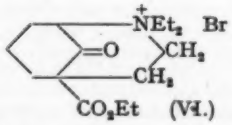
The literature reveals only one " synthesis " of such a ring system. Farmer and Ross (*J.*, 1926, 3235) obtained (II) by Michael addition of ethyl cyanoacetate to 3-methyl-Δ^2-*cyclo*hexenone, and on boiling it with 15% hydrochloric acid obtained in quantitative yield an acidic substance giving an intense ferric chloride colour to which they ascribe the structure (III). This structure is most improbable for the following reasons: (*a*) it violates Bredt's rule, which states that the carbon atom at the bridge head of a bridged ring system cannot bear a double bond; (*b*) it is a derivative of malonic semi-amide and should thus not give a ferric chloride reaction; and (*c*) it is difficult to believe that a compound of such structure would be stable to boiling mineral acid. There is thus no evidence that the ring system (IV) has ever been synthesised heretofore, and, to save difficulties with the cumbrous and obscure *bicyclo*aza nomenclature, it is suggested that it be given the trivial name " morphan " (a suggestion for which I am indebted to Sir Robert Robinson) and be numbered as shown.



(IV.)



(V.)

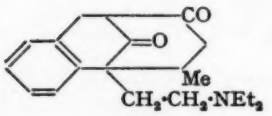


(VI.)

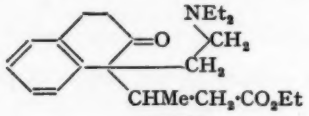
Ethyl sodio*cyclo*hexanone-2-carboxylate refluxed with diethyl-β-chloroethylamine in toluene solution gave *ethyl* 2-β-*diethylaminoethyl*cyclo*hexanone*-2-*carboxylate* (V), which was converted by bromine in the cold into the hydrobromide of the 6-bromo-derivative. This was not isolated, but immediately treated with sodium bicarbonate solution to give the free base which on heating in toluene afforded *ethyl* 9-*keto*-2-*ethylmorphan*-5-*carboxylate ethobromide* (VI) in small yield. The ultra-violet absorption spectrum of the substance (examined by Dr. F. Strauss) showed no αβ-unsaturated carbonyl absorption, indicating that it was not the isomeric hydrobromide of ethyl 2-β-diethylaminoethyl-Δ^5-*cyclo*hexenone-2-carboxylate.

The synthesis of the morphan ring system having been shown to be practicable along these lines it was decided to perform similar operations on β-tetralones in the hope of obtaining the benzmorphan system occurring in morphine. 2-Keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Barltrop, *J.*, 1946, 958) and ethyl crotonate in the presence of sodium ethoxide yielded a mixture of 2 : 9-*diketo*-4-*methyl*-5-β-*diethylaminoethyl*-6 : 7-*benzo*bicyclo[3 : 3 : 1]*nonane*

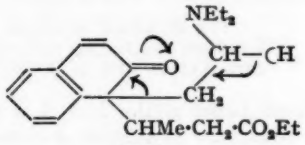
(VII) and 2-*keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxy*isopropyl-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII). The latter substance when brominated and treated with alkali as in the *cyclo*hexanone series gave a small yield of a salt which appeared to be *diethylvinylamine hydrobromide*. This presumably arose by loss of hydrogen bromide from the bromo-β-tetralone to give (IX) in which



(VII.)



(VIII.)

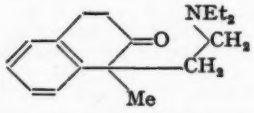


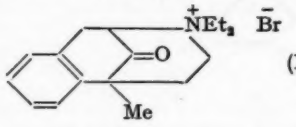
(IX.)

the tendency to become aromatic is so great as to cause extrusion of the basic side-chain, a phenomenon closely parallel to the well-known elimination of the ethanamine side-chain in the morphine group of alkaloids when they assume an aromatic structure. At this stage it seemed that further work was called for on the process of cyclisation and more accessible materials were chosen.

2-Keto-1-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (Cornforth, Cornforth, and Robinson, *J.*, 1942, 690) was alkylated with diethyl-β-chloroethylamine and sodamide giving 2-*keto*-1-*methyl*-1-β-*diethylaminoethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (X). In the previously described experiments, the amino-ketone free base had been brominated, but as a variant (X) was converted into its hydrobromide, and this, without further purification, was brominated in chloroform solution. On washing with sodium bicarbonate solution, the free base was liberated and rapidly cyclised in the cold to 9-*keto*-5-*methyl*-2-*ethyl*-6 : 7-*benzomorphan ethobromide* (XI).

(X.)





(XI.)

The substance did not decolorise potassium permanganate solution and thus cannot be the isomeric β-naphthol derivative.

Experiments are in progress having as their object the synthesis of the tertiary amine analogues of (XI) and the cyclisation of the third carbon ring of the morphine molecule.

Experimental.

Ethyl 2-β-*Diethylaminoethyl*cyclo*hexanone*-2-*carboxylate* (V).—Ethyl *cyclo*hexanone-2-carboxylate (34·3 g.; Kötz and Hesse, *Annalen*, 1906, **350**, 210; 1907, **358**, 198) was added with agitation and cooling to powdered sodium (4·6 g.) under toluene (100 c.c.). When reaction had ceased the sodio-derivative was refluxed for 6 hours with a toluene solution of diethyl-β-chloroethylamine [prepared by basifying the hydrochloride (54 g.) with potassium carbonate, extracting several times with toluene, and drying over potassium carbonate]. The reaction mixture was extracted with hydrochloric acid, the aqueous layer basified with sodium hydroxide, and the liberated amine isolated with ether and distilled. The *keto-ester* (33 g.) was collected at 164°/11 mm. (Found: C, 66·5; H, 10·3; N, 5·4. $C_{15}H_{27}O_3N$ requires C, 66·9; H, 10·0; N, 5·2%).

9-*Keto*-5-*carbethoxy*-2-*ethylmorphan Ethobromide* (VI).—The above amine (1·1 g.) dissolved in ligroin (5 c.c.) was cooled to 0° and treated gradually with a cooled solution of bromine (0·65 g.) in ligroin (3 c.c.). Ice-water (3 c.c.) was added to dissolve the oily hydrobromide, and separated from the ligroin which was washed with ice-water (3 c.c.). The combined aqueous extracts were immediately treated with a solution of sodium bicarbonate (1 mol.) and rapidly extracted with toluene. The extract was dried and heated on the steam-bath for 16 hours. A brown oil was deposited, followed after several hours by plate-like crystals. The *ethobromide* (*ca.* 10 mg.), m. p. 201°, was collected and washed with ether (Found: C, 51·4; H, 7·5; Br, 22·9. $C_{15}H_{24}O_3NBr$ requires C, 51·7; H, 7·5; Br, 23·0%).

2-*Keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxy*isopropyl-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII).—2-Keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (14·2 g., Barltrop, *loc. cit.*) and ethyl crotonate (7·1 g.) were added to a solution of sodium (1·33 g.) in dry ethanol (25 c.c.). The mixture was refluxed for 4 hours and left overnight; water (120 c.c.) and glacial acetic acid (3·0 g.) were then added and the products isolated with ether and distilled. The following fractions were obtained: (*a*) b. p. 140°/0·04 mm.; (*b*) b. p. 140—165°/0·04 mm. (mainly 150°); (*c*) b. p. 165—190°/0·04 mm. On refractionation, (*a*) and (*b*) gave unchanged 2-keto-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene and 2 : 9-*diketo*-4-*methyl*-5-β-*diethylaminoethyl*-6 : 7-*benzo*bicyclo[3 : 3 : 1]*nonane* (VII), a yellow oil, b. p. 160° (bath)/0·01 mm. (Found: C, 76·1; H, 8·9. $C_{20}H_{27}O_2N$ requires C, 76·7; H, 8·6%), and a high boiling residue, which was added to (*c*) and refractioned. 2-*Keto*-1-β-*diethylaminoethyl*-1-β-*carbethoxyisopropyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VIII) (6 g.), a viscous yellow oil, was collected at 175°/0·1 mm. (Found: C, 73·6; H, 9·1. $C_{22}H_{33}O_3N$ requires C, 73·5; H, 9·2%).

Attempted Cyclisation of (VIII).—Bromine (0·32 g., 0·002 mol.) dissolved in toluene (5 c.c.) was added

to a cooled solution of the above amino-keto-ester (0·72 g., 0·002 mol.) in toluene (5 c.c.). Sodium carbonate solution was added, the mixture shaken, and the toluene layer separated and combined with the toluene extract of the aqueous layer. After being dried ($MgSO_4$), the toluene solution (*ca.* 50 c.c.) was dried azeotropically by distilling a few c.c. under reduced pressure and then heated on the steam-bath. A few colourless plate-like crystals separated and were collected and crystallised from ethanol–ether (Found: Br, 44·4. $C_8H_{13}N,HBr$ requires Br, 44·4%). The substance decolorises acidified potassium permanganate solution instantaneously.

2-Keto-1-methyl-1-β-diethylaminoethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (X).—2-Keto-1-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene (16 g., Cornforth, Cornforth, and Robinson, *loc. cit.*), diethyl-β-chloroethylamine (14·3 g.), and toluene (80 c.c.) were stirred in an atmosphere of nitrogen, and powdered sodamide (4·3 g.) was added gradually with external cooling. When the initial exothermic reaction had ceased, the temperature of the reaction mixture was slowly raised to 90° during 2 hours, maintained there for 5 hours, and finally refluxed for 1 hour. After cooling, the mixture was extracted with hydrochloric acid, the acid extract was washed with ether and basified, and the liberated amines were isolated with ether and distilled. The *amino-ketone* (10 g.), a viscous yellow oil, was collected at 120°/0·18 mm. (Found: C, 78·8, 78·2; H, 9·8, 9·6; N, 5·55, 5·4. $C_{17}H_{25}ON$ requires C, 78·8; H, 9·65; N, 5·4%). The picrate, picrolonate, oxalate, and flavianate were all oils.

9-Keto-5-methyl-2-ethyl-6 : 7-benzomorphan Ethobromide (XI).—The above amino-ketone (2·6 g., 0·01 mol.) dissolved in dry ether was converted into the gummy hydrobromide which was washed thrice with ether and dissolved in chloroform (10 c.c.). After cooling to 0° a cooled solution of bromine (1·6 g.) in chloroform (5 c.c.) was added dropwise with cooling. A cooled solution of sodium bicarbonate (3 g.) was added, and the mixture was shaken and separated. The chloroform layer was dried and then evaporated at room temperature under reduced pressure giving an orange gum insoluble in ether. This was dissolved in chloroform and concentrated under reduced pressure. On keeping, crystals (*ca.* 0·3 g.), m. p. 203° (decomp.), separated and were collected. The *ethobromide* crystallised from much *iso*propanol in colourless microscopic needles, m. p. 212° (decomp.) (Found: C, 60·0; H, 7·25; Br, 24·2. $C_{17}H_{24}ONBr$ requires C, 60·3; H, 7·1; Br, 23·7%). The substance is soluble in water and does not decolorise potassium permanganate solution.

The author wishes to thank Sir Robert Robinson for his interest in this work.

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82. *The Redistribution and Desorption of Adsorbed Gases.*

By R. F. BARROW, C. J. DANBY, J. G. DAVOUD, C. N. HINSHELWOOD, and L. A. K. STAVELEY.*

The distribution of adsorbed gases in columns of adsorbent and their redistribution and eventual desorption on passage of a stream of air are relevant to several problems of general importance. The present paper gives experimental results on the distribution of various gases on charcoal columns during progressive saturation, and for the changes in the distribution of adsorbed gas caused by diffusion or by the passage of an air stream. In the latter case the variations with time in the concentration of gas in the effluent stream are also considered.

It is shown that the behaviour of these systems can be calculated with considerable accuracy from a knowledge of the adsorption isotherm by a process of successive approximation. The calculations involve the assumption—not predictable theoretically, but fully justified by the agreement with experiment—that adsorption equilibrium between gas and solid is maintained throughout.

THE removal of gases and vapours from air streams by solid adsorbents sometimes takes the form of a definite chemical reaction, as, for example, when active charcoal destroys, by oxidation, hydrogen sulphide and certain other gases. Such processes are irreversible and have been considered in a previous paper (*J.*, 1946, 918). On the other hand, if the gas is held on the solid by simple adsorption, the process is reversible and gas may be desorbed into the air stream. Some of the phenomena which arise under these conditions are discussed in the present paper.

The processes of redistribution and desorption are of interest in connexion with several practical problems. One is that of solvent recovery. Another is that of the safe use of respirators which have had a short exposure to toxic gases and are subsequently breathed through, either immediately, or after an interval in which diffusion may occur. The results given in this paper show that the actual rates of redistribution and desorption may vary by factors of several hundred from one gas to another. Nevertheless the behaviour can be quantitatively predicted from a knowledge of the adsorption isotherm of the gas. The calculations depend upon an auxiliary assumption, not predictable, but fully justified by

* The results given in this paper are taken from a very much greater volume of experimental material—much of it obtained in connexion with specific practical problems and contained in reports to the Ministry of Supply, with the following additional co-authors: G. T. Kennedy, J. J. Kipling, J. A. E. Moy, and J. H. Nicholls.

experiment, namely, that throughout adsorption and desorption—within the range of experimental conditions employed—adsorption equilibrium between gas phase and solid is maintained.

The system whose physical chemistry is considered is essentially a column of granular adsorbent into which a certain amount of adsorbable gas is first carried by a stream of air. The gas stream is passed for only a fraction of the time required to saturate the column, pure air being then passed through so that redistribution and desorption of the gas occur. The initial treatment of the column with the gas–air stream may be followed by a period of rest during which redistribution can occur by diffusion, before the resumption of the air stream. The methods of calculation employed are, however, applicable to a wider range of problems than these.

The complete equations for the rate of change of concentration of the gas as a function of time and position in the column can be written down, but they are, in general, quite insoluble. In the special case where the adsorption isotherm of the gas on the solid is a straight line a cumbrous solution in series may be obtained (Wicke, *Kolloid-Z.*, 1940, **93**, 129). Adsorption isotherms are, however, usually not linear, and in fact can rarely be represented by any simple equation. Since the phenomena of desorption are found to depend to a remarkable extent on the *precise shape* of the isotherm, the treatment of the problem by direct solution of the differential equation is not practicable.

The theoretical treatment is based on the following principles: (1) The column is divided into a series of small finite elements of length which are treated as though differential methods could be accurately applied to them. In the same way a series of small time intervals are treated as differentials. By suitable choice of the magnitude of these column elements and time intervals a compromise may be achieved between loss of accuracy on the one hand and excessive laboriousness of calculation on the other. (2) Equilibrium between each element of the column and the gas stream is assumed to be attained very rapidly. The justification of this assumption will appear later, where it will be seen that equilibria, rather than rates of attainment of equilibria, govern the observed effects. (3) The equilibrium assumed is that represented by the *actual experimentally determined* isotherm.

In discussing desorption we must consider the following phases:

(*a*) The adsorption phase: in which the gas is carried into the column by the air stream and adsorbed—to the greatest extent—in the initial layers. The distribution of gas in the column at the end of this phase is the initial distribution for (*b*).

(*b*) The redistribution phase: in which the passage of pure air leads to desorption from the initial layers and progressive transference of the gas along the column.

(*c*) The desorption phase: in which this transferred gas reaches the final layer of the column and is desorbed into the effluent stream.

After considering experimental methods, we shall discuss these stages in turn. In each section, experimental results relating to columns of active charcoal and the gases hydrogen cyanide, carbon tetrachloride, cyanogen chloride, and water will be compared with the behaviour calculated from the above principles.

Experimental Methods.

The experiments fall into four groups: (i) Investigation of the distribution of gases along charcoal columns during adsorption and desorption. (ii) Measurement of the changes in effluent concentration with time during the passage of air through columns previously exposed to gas streams. (iii) Investigation of the redistribution of adsorbed gas under the influence of diffusion alone. (iv) Determination of the adsorption isotherms of the different gases on charcoal.

(i) *Distribution of Adsorbed Gases along Charcoal Columns during Adsorption and Desorption.*—All experiments were made at approximately 20° with an unimpregnated commercial charcoal produced from briquetted coal. The charcoal was graded 7—18 mesh B.S.S. sieve sizes, and was dried before use. Gas compositions are stated in volume per cent.

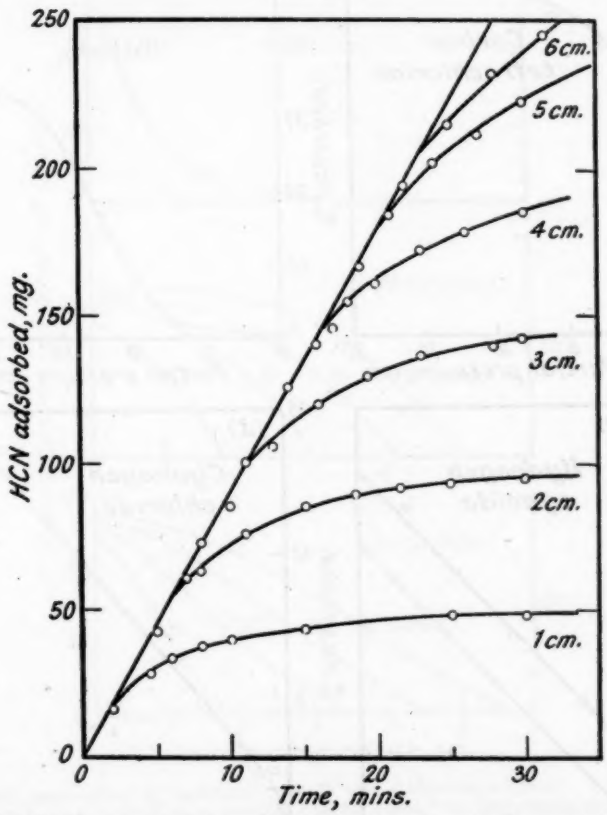
(a) *Hydrogen cyanide.* The adsorption of hydrogen cyanide was followed by direct weighing. Its distribution was determined by the application of the following principle. If an air stream containing an adsorbable gas is passed through a layer of adsorbent 1 cm. in length, then the gain in weight of this layer will be identical with the adsorption which would have taken place in the first cm. length of a long column under the same conditions. Similarly, the difference between the uptake of columns 2 cm. and 1 cm. in length gives the adsorption in the second 1 cm. section of a long column. By successive measurements on columns of increasing length the complete distribution of gas at any stage may be obtained. The curves in Fig. 1 show the gain in weight of columns of charcoal from 1 cm. to 6 cm. in length during the passage of 1·0% hydrogen cyanide (800 c.c./min. through a 2 cm. diameter column). The vertical distance between two curves at any given time gives the amount of gas adsorbed on the corresponding 1 cm. length of the column. We can thus obtain complete information about the changes in distribution of the gas in the column as adsorption proceeds.

In plotting distribution curves (such as those shown in Fig. 4), the amount of adsorbed gas has been averaged over each successive cm. length of the column at a series of successive times. The centre of gravity of the gas adsorbed on any section has been assumed to be at the mid-point. This will only be strictly true when the section has become saturated : until then the centre of gravity of the adsorbed material will be nearer the end at which the gas enters. The error introduced by plotting the gas concentrations at the mid-point of each section is small and has been neglected.

In experiments on desorption, a relatively small amount of gas is admitted to the column, and the changes in its distribution on passage of a stream of pure air are followed. This can be done in exactly the same way by carrying out measurements on columns of different length.

(b) *Carbon tetrachloride.* The distribution of carbon tetrachloride was investigated by the use of a column of adsorbent which could be separated into sections. By weighing each section of the column individually at intervals during adsorption and desorption the amount of carbon tetrachloride on it at any instant could be determined.

FIG. 1.



The adsorption of hydrogen cyanide from a 1% stream by charcoal columns of different lengths.

(c) *Cyanogen chloride.* For this gas, instead of determining the increase in weight of the adsorbent, the amount of gas escaping from the end of the column was estimated by chemical analysis. Subtraction from the known input of gas gave the amount retained at any instant.

(d) *Water.* A similar method was used with water vapour, which was estimated by passing the effluent stream through a calcium chloride tube weighed at intervals. The values obtained in this way for the water adsorbed were checked by direct weighing of the column itself.

(ii) *Determinations of Effluent Concentrations.*—After appropriate treatment of the column with the gas under investigation, a stream of pure air was passed through at a standard rate (200 c.c./min. for a column 1 cm. in diameter). The concentration of the gas in the effluent was then determined at successive times by a suitable analytical method. Water and carbon tetrachloride were estimated gravimetrically; hydrogen cyanide by adsorption in sodium hydroxide solution, buffering to a controlled pH, and titration with standard iodine; cyanogen chloride by conversion into ferric thiocyanate which was determined colorimetrically. The experimental arrangements were very similar to those described in a previous paper (*J.*, 1946, 918).

(iii) *The Redistribution of Gases by Diffusion.*—The experimental methods were similar to those described under (i).

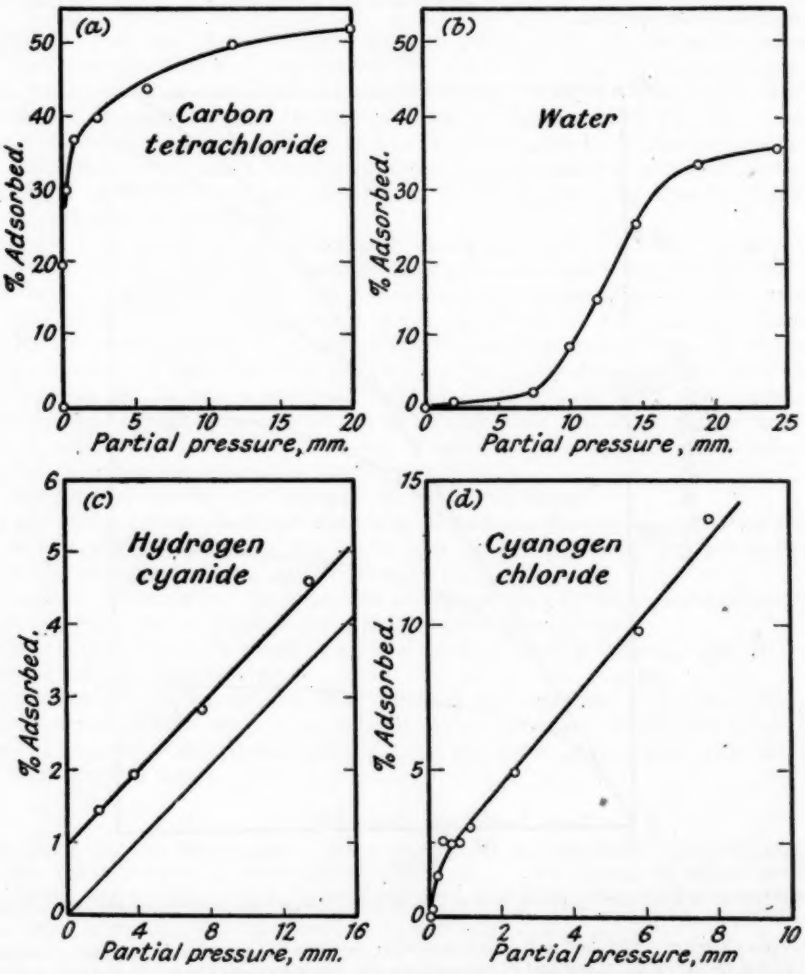
(iv) *The Determination of Adsorption Isotherms.*—The isotherms of carbon tetrachloride and cyanogen

chloride were determined by use of a quartz-spring adsorption balance. The measurements were made either directly, or by the method of Allmand and Burrage (*J. Soc. Chem. Ind.*, 1928, **47**, 369).

Water isotherms were measured by a static method. Small amounts of charcoal in wire-gauze containers were allowed to come to equilibrium with the water vapour over a series of saturated salt solutions at 25°. The amount of water taken up was determined by weighing. The vapour pressures of the solutions were taken from Obermiller (*Z. physikal. Chem.*, 1924, **109**, 145).

The hydrogen cyanide isotherm called for special treatment. For lower pressures it was determined by passing HCN–air streams of various concentrations through charcoal till saturation was reached, and measuring the increase in weight. For higher pressures the quartz adsorption balance was employed.

FIG. 2.



Adsorption isotherms for carbon tetrachloride, water, hydrogen cyanide, and cyanogen chloride on active charcoal.

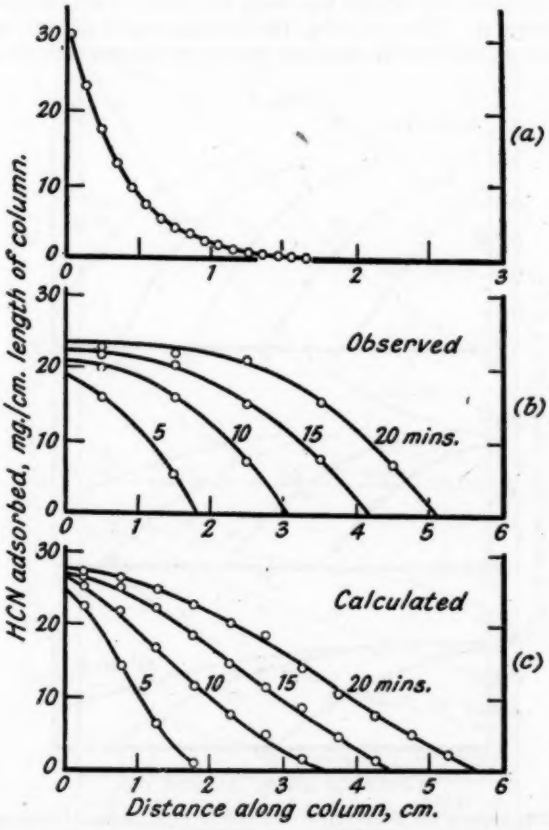
The experimentally determined isotherm shows an apparent intercept on the weight axis. This is illusory and is due to slow reaction of the adsorbed hydrogen cyanide; the intercept represents the amount of the gas which has reacted in the time taken for the experiment. The precise form of curve obtained is thus to some extent a function of the time for which the gas has been in contact with the charcoal, and is not really that of a true isotherm. In subsequent calculations, where the phenomenon under consideration involves prolonged contact of gas and charcoal, this experimental curve showing the intercept has been used. It makes allowance, even if a somewhat arbitrary one, for loss of gas in chemical reaction. For the calculation of the initial penetration of gas into the column, where the gas and charcoal have been in contact for only a very short period of time, a better approximation to the true isotherm was taken to be a line drawn parallel to the experimental curve, but passing through the origin.

The experimental isotherms for the four gases used in the present series of experiments on the charcoal employed are given in Fig. 2.

The Distribution of Adsorbed Gas in Charcoal Columns during Adsorption.

The phenomena which arise during the desorption of gas from a partially saturated column on passage of air are dependent on the initial distribution of the adsorbed gas in the column. We must first, therefore, consider the distribution of adsorbed gases which have been taken up from air streams under various conditions.

FIG. 3.



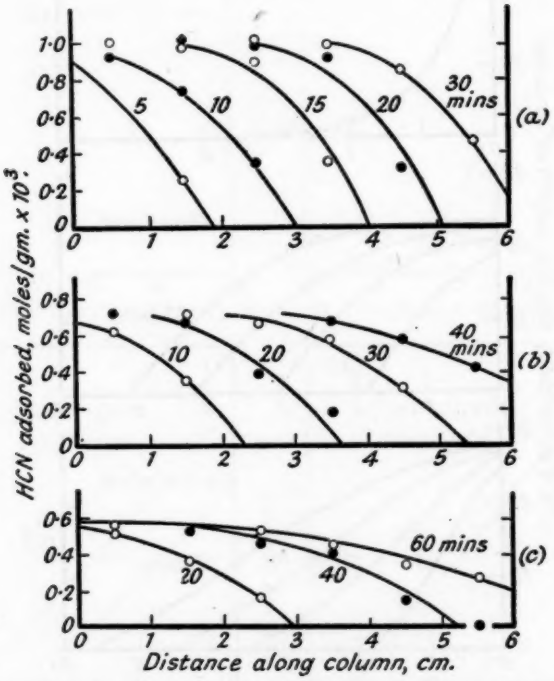
(a) *Calculated initial penetration of hydrogen cyanide into a charcoal column.* (b) *Experimental curves showing the distribution of* HCN *in a charcoal column during the progressive saturation of the column.* (c) *Calculated distributions of* HCN *for comparison with* (b).

(i) *The Attainment of Equilibrium between Charcoal and Gas.*—The whole treatment adopted in this paper depends on the assumption that equilibrium is maintained, and the agreement with experiment is a vindication of that assumption. One direct way of illustrating the extent to which adsorption equilibrium is attained during the passage of a gas through a charcoal column may be derived from curves such as those in Fig. 1. The slope at any point gives the rate of adsorption of gas. The difference between this value and the rate at which gas is being admitted is the rate at which gas is escaping from the end of the column. The rate at which gas is entering the nth unit-length section of a column is the rate at which it would have been escaping from the end of a column $(n - 1)$ units long after the same time. We can therefore obtain the rates at which gas is entering and leaving each section of the column, and hence the mean concentration in each section at any instant. The total amount of gas adsorbed in each section at any moment is also known. We can therefore plot the amount of gas adsorbed against the mean partial pressure. If the charcoal were in equilibrium with the gas this curve would be identical with the adsorption isotherm. Fig. 6 is an example of the type of result obtained in

this way and shows how nearly equilibrium between charcoal and gas is maintained throughout adsorption and desorption—at least under the conditions of flow-rate and concentration employed here.

(ii) *The Method of Calculation of the Adsorption of Gases in Charcoal Columns.*—From a knowledge of the adsorption isotherm the changes in the distribution of a gas during progressive saturation of the column may be calculated. The column is considered as a number of finite elements of length. The first volume-element of the gas stream is assumed to reach instantaneous equilibrium with the first element of the column. Gas is adsorbed, so that the concentration of gas leaving the element will be less than the initial concentration. Hence the second element of the column will adsorb less than the first. Each successive element adsorbs less than the one preceding it. Theoretically, the column would have to be of infinite length to reduce the concentration to zero, but in practice the concentration falls to a negligible value in a

FIG. 4.



Distribution changes accompanying the progressive saturation of a charcoal column by HCN *at* (a) 1·0%, (b) 0·5% *and* (c) 0·25%.

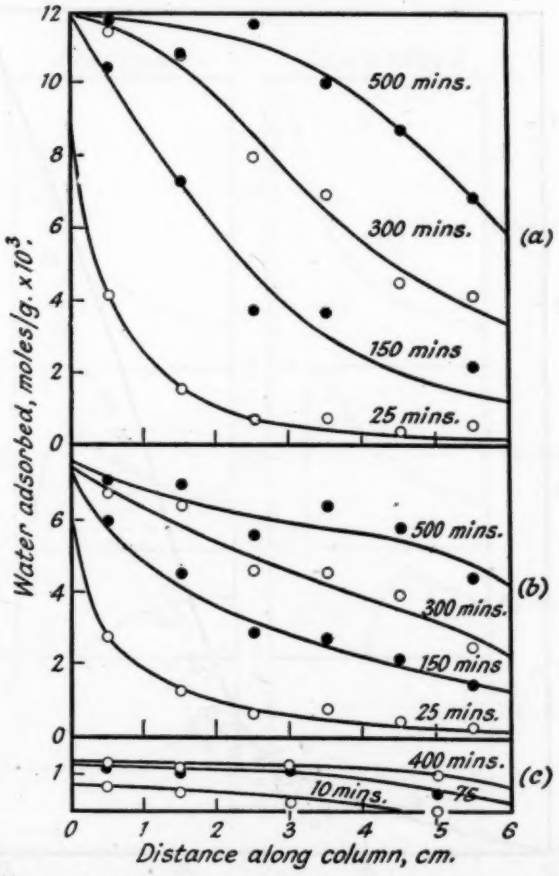
definite distance. This immediate penetration of gas may be calculated by the following process of successive approximation:

A volume of the gas stream of known initial concentration (for example, that passing in the first minute of flow into the column) is assumed to come to adsorption equilibrium with the first unit section of the column. We require to find a value for the amount of gas adsorbed such that it will be in equilibrium at the partial pressure of the gas remaining in the stream. If the gas concentration were unchanged by the adsorption, the isotherm would give directly a value for this amount. This will be an *upper limit* for the adsorption. Subtraction of this from the total initial amount in the volume-element gives a *lower limit* for the final gas concentration, which, from the isotherm, will give a *lower limit* for the adsorption. The value required will lie between these extreme values: to a first approximation it will be given by their mean. The use of this to subtract from the initial amount of gas gives a better value for the amount left in the stream, and the amount adsorbed which would be in equilibrium with this partial pressure is read off from the isotherm. The mean of this value and the previous approximation is then taken, and the process repeated. Eventually a pair of values for the adsorbed and unadsorbed gas are found which correspond to equilibrium according to the experimental isotherm.

The equilibrium partial pressure for the first element of the column is the initial concentration for the second. The above calculations are repeated for each succeeding section until the residual partial pressure reaches a negligible value. This gives the distribution of the gas in the column at the end of the first minute of flow of the gas stream. Taking this distribution as a new initial state we can consider the passage of the stream for a further minute. By repeating this process for a whole series of successive time intervals we can calculate the distribution changes during the gradual approach of the column to saturation.

(iii) *A Comparison of Experimental and Calculated Results.*—(a) *Hydrogen cyanide.* Fig. 3(*a*) shows the amounts of hydrogen cyanide adsorbed by each successive cm. length of a charcoal

FIG. 5.



Distribution changes accompanying the progressive saturation of a charcoal column by water vapour at (a) 1·9%, (b) 1·6% *and* (c) 0·9%. (*The immediate penetration through the column is to be noted.*)

column 2 cm. in diameter after the first minute of passage of 1·0% hydrogen cyanide, calculated from the isotherm [Fig. 2(*c*)] by the method described. Fig. 3(*c*) gives the calculated distribution of the gas at five-minute intervals during the saturation of the column. Experimental results for comparison with Fig. 3(*c*) are given in Fig. 3(*b*). The agreement is satisfactory as regards the time scale for the desorption.

Fig. 4 gives the experimental results for the changes in distribution during the saturation of charcoal columns by 0·25%, 0·5% and 1·0% hydrogen cyanide. The lower the initial concentration at which a given amount of hydrogen cyanide is passed into the column, the greater the depth to which it penetrates.

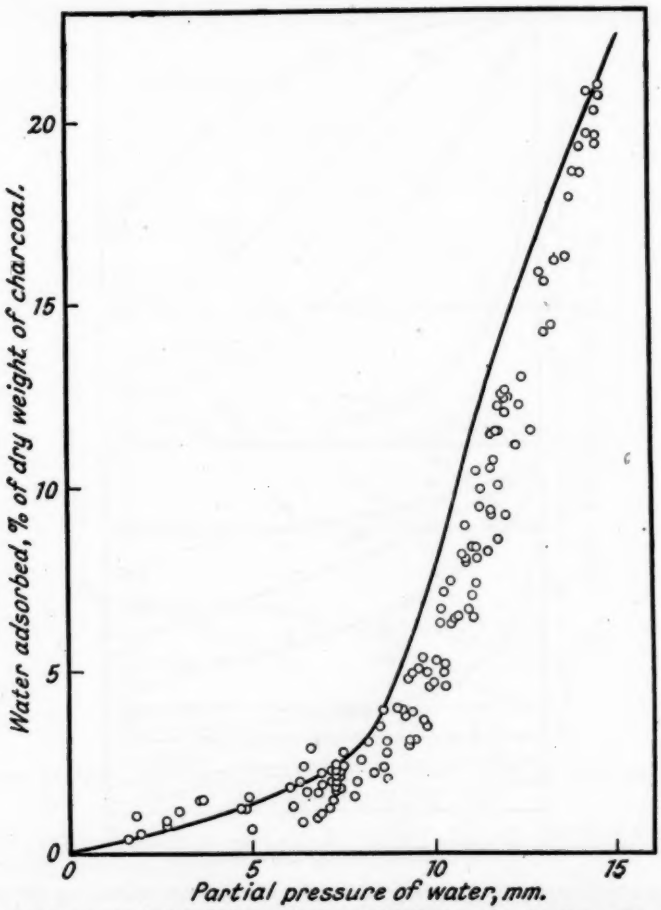
(b) *Carbon tetrachloride.* Experiments were made to determine the initial distribution of carbon tetrachloride along a column when a given amount was carried in by the air stream at two different initial concentrations (2% and 0·2%). The distribution is very nearly independent of

the initial concentration. The experimental adsorption isotherm for carbon tetrachloride, given in Fig. 2(*a*), shows that there is rather little variation in the equilibrium amount adsorbed over the concentration range 2% to 0·2%. The observed constancy of distribution is therefore in agreement with the isotherm.

By the method of successive approximation explained above, the distribution of carbon tetrachloride during passage of a 0·2% stream was calculated, and gave good agreement with experimental results.

(c) *Water.* The isotherm for the adsorption of water on charcoal is of an unusual shape [Fig. 2(*b*)]. At partial pressures below about 6 mm. of water vapour (0·8%), the amount

FIG. 6.



Adsorption isotherm for water inferred from observed distributions in the flow system (marked points). The continuous line gives the isotherm corresponding to complete equilibrium.

adsorbed is small and increases only slowly with pressure. Between about 10 mm. and 20 mm. it increases rapidly, and at 20 mm. (2·5%) saturation is nearly reached. The distribution of water in charcoal columns was investigated with air streams containing water at partial pressures corresponding to three significantly placed points on the isotherm. Two (1·9% and 1·6%) are on the steeply rising section. The third (0·9%) is on the lower part, corresponding to a much lower percentage adsorption. The experimental results are given in Fig. 5, where the same scale is used for all concentrations. The shape of the wave-front in the column changes from concave at small adsorptions to convex as saturation is approached.

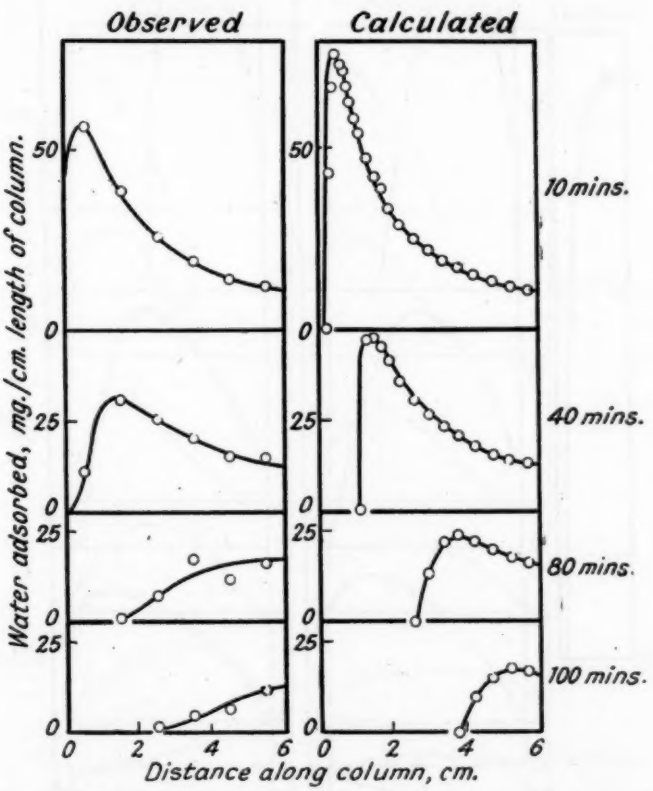
The distribution of water obviously differs greatly from that of the other vapours considered in this paper. There is immediate penetration of water vapour right through the column. This is a consequence of the very small slope of the initial part of the isotherm. Changes in

the concentration of water vapour in the stream have more effect on the total amount taken up in the column than on its distribution.

The distribution of water along the column was calculated from the isotherm by a process of successive approximation similar to that already explained. With the data from which Fig. 5 was derived, the values plotted in Fig. 6 were calculated, the isotherm being shown as a continuous line. The calculated points lie quite near to the true isotherm, indicating that in the various distribution experiments there has been a close approach to equilibrium.

(d) *Cyanogen chloride.* The distributions of cyanogen chloride in a charcoal column after passage of 1·0% for 4 minutes and of 0·1% for 40 minutes were determined. A given amount of gas was found to be distributed over a greater length of the column when admitted at a lower

FIG. 7.



Changes in the distribution of water in a charcoal column on passage of a stream of air.

concentration. In its behaviour, therefore, cyanogen chloride bears a closer resemblance to hydrogen cyanide than to water or carbon tetrachloride.

The calculated distribution of cyanogen chloride was in good agreement with the experimental results.

The Change in Distribution with Time during Desorption.

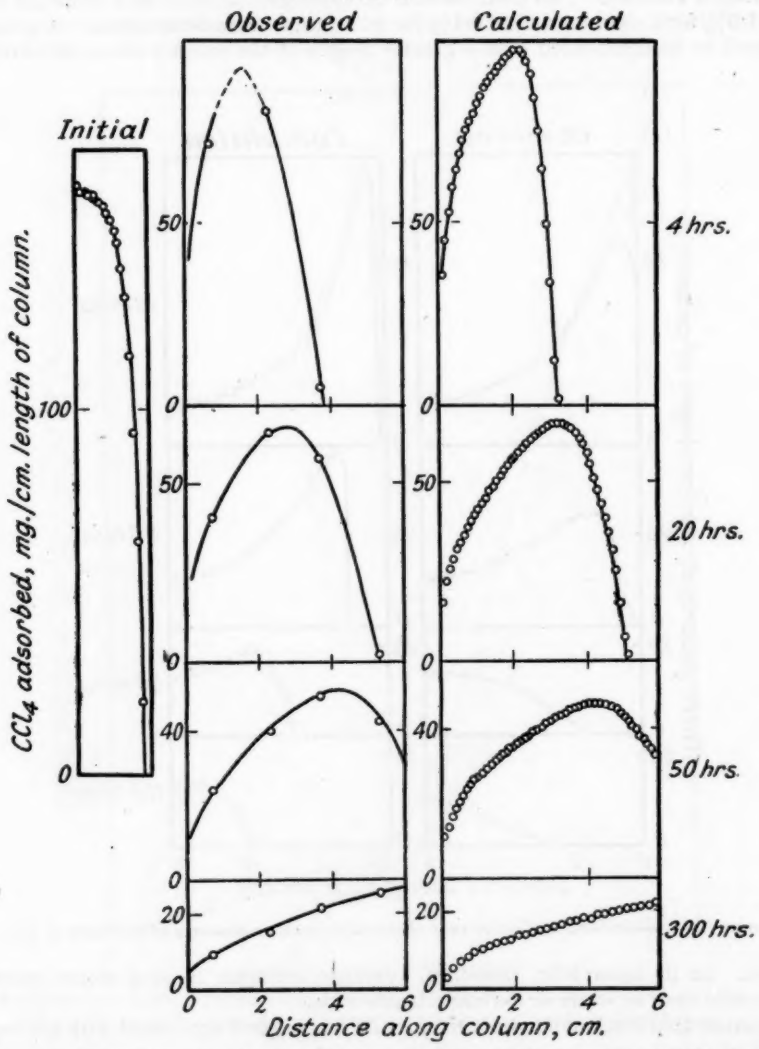
In this section we consider a charcoal column on to which a certain amount of gas has already been carried, and investigate the changes in distribution caused by subsequent passage of a stream of pure air.

Experiments with the four gases previously considered showed that the respective times required for the transference of comparable amounts differed by whole orders of magnitude. These very diverse rates of transfer can, however, be satisfactorily calculated from the isotherms by an extension of the method already described. To illustrate the procedure, the transfer of water from a single section of a column in a single interval of time will be calculated.

Consider the first 1 mm. section of a column on which are adsorbed 9·50 mg. of water. We

wish to find the water content of this section after the passage of dry air at the standard rate for 3 minutes. The amount initially adsorbed corresponds to 21·0% water on the charcoal, and the initial vapour pressure of water over the section is therefore 14·46 mm. [from the isotherm, Fig. 2(*b*)]. If this pressure were maintained for 3 minutes, the charcoal would lose 8·16 mg. to the stream, leaving 1·34 mg. on the charcoal : this is a ***maximum*** estimate for the desorption. A water content of 1·34 mg. corresponds to 2·97% and a vapour pressure of 7·97 mm., which

FIG. 8.



Changes in the distribution of carbon tetrachloride in a charcoal column on passage of a stream of air.

would lead to the ***minimum*** estimate for desorption, namely, 4·49 mg., leaving 5·01 mg. on the charcoal. Proceeding in this way :

9·50 mg. on charcoal ≡ 14·46 mm., or 8·16 mg. desorbed : 1·34 mg. on charcoal.
1·34 mg. on charcoal ≡ 7·97 mm. or 4·49 mg. desorbed : 5·01 mg. on charcoal.
½(1·34 + 5·01) = 3·18 on C ≡ 9·78 mm. or 5·52 mg. desorbed : 3·98 mg. on charcoal.
½(3·98 + 3·18) = 3·58 on C ≡ 10·60 mm. or 5·98 mg. desorbed : 3·52 mg. on charcoal.

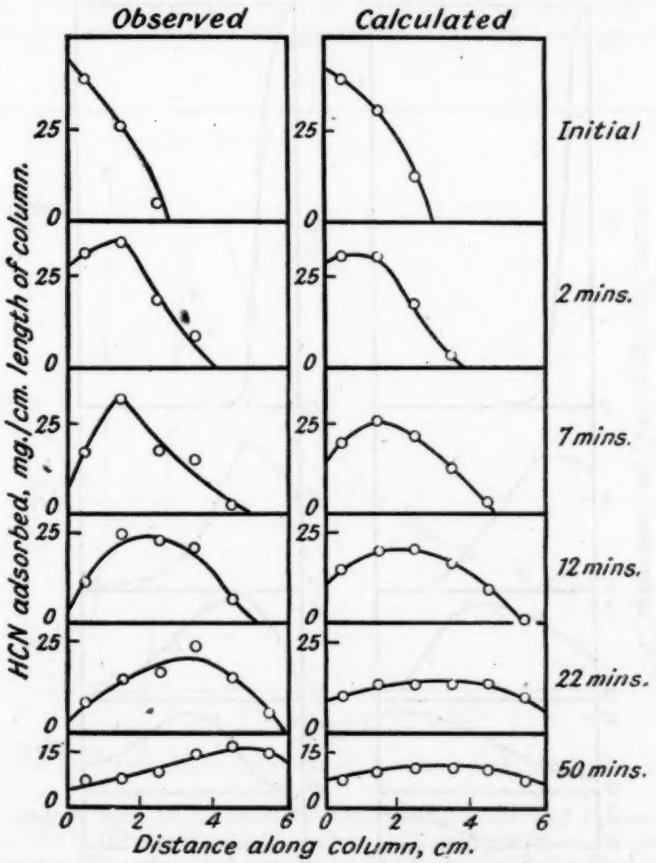
The final amount of water on this section is found in this way to be 3·55 mg., so that the air stream has picked up 5·95 mg. to give a mean partial pressure of water of 10·50 mm. This is the initial concentration of water vapour offered to the second element in the column.

Calculations of this type carried out for each successive element in the column give the transfers of water from section to section in the 3-minute interval chosen. By repeating the series for a succession of such intervals we eventually obtain a picture of the whole of the desorption process.

These calculations have been made for the four gases : water, carbon tetrachloride, hydrogen cyanide, and cyanogen chloride. The calculated curves for the distribution changes during the desorption are compared with the experimental results in Figs. 7, 8, 9, and 10. The results obtained will now be considered briefly.

Water.—On passing dry air into a charcoal column previously treated with a wet air stream for a short time, a steep maximum is rapidly set up in the distribution. This maximum moves

FIG. 9.



Changes in the distribution of hydrogen cyanide in a charcoal column on passage of a stream of air.

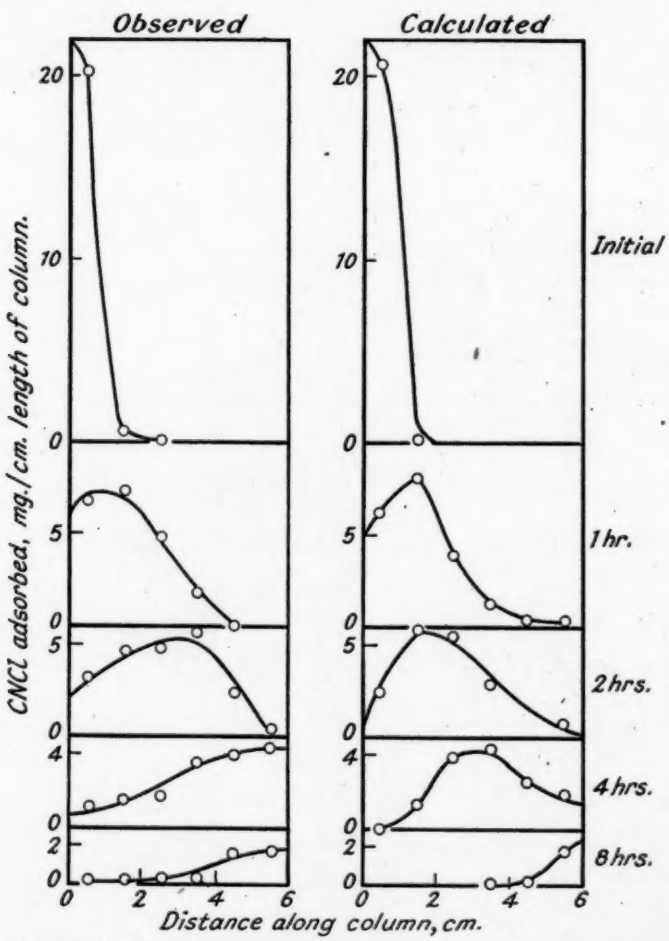
through the column, decreasing in height and becoming more rounded. The amount of water in the later sections of the column remains almost constant until about 80% of the total water has been desorbed : this results in an almost constant concentration of water vapour in the effluent during this time. The calculated distributions agree well with the experimental data, except that the calculated maximum concentrations are somewhat greater than those observed—probably because the experimental results are averages of concentrations over 1 cm. sections while the calculations are based on much shorter elements. The areas under the two sets of curves, however, correspond closely, and the times for complete desorption—about 115 minutes (calculated) and 135 minutes (observed)—are in good agreement.

Carbon Tetrachloride.—The adsorption isotherm is such that, even when quite large amounts are adsorbed, the vapour pressure is small. The leading edge of the distribution curve of adsorbed carbon tetrachloride is therefore initially very steep. The change in the form of the

distribution with time during the passage of air is qualitatively very similar to that observed with water. The time scale is, however, vastly greater. As will be seen from Fig. 8, appreciable amounts of carbon tetrachloride still remain in the intial layers of the column after air has been passing for 300 hours. Sensibly complete desorption is only attained after about 600 hours. Comparison of the experimental and calculated results reveals very good agreement.

Hydrogen Cyanide.—The change of distribution with time during desorption of hydrogen cyanide is similar to that observed with the other gases, but the calculations give a rather greater rate of progress than is actually observed. This discrepancy is almost certainly to be

FIG. 10.



Changes in the distribution of cyanogen chloride in a charcoal column on passage of a stream of air.

attributed to chemical reaction of the hydrogen cyanide which proceeds hand in hand with desorption. Even so, the calculations predict a time-scale for desorption which is fairly close to that observed experimentally.

Cyanogen Chloride.—For cyanogen chloride the results indicate a behaviour intermediate between that of hydrogen cyanide on the one hand and carbon tetrachloride on the other. Thus the time-scale for desorption under the conditions employed is of the order of 10 hours. This is to be compared with about 1 hour for hydrogen cyanide and over 300 hours for carbon tetrachloride. The calculations give the correct order of magnitude of this time-scale, and reproduce fairly well the changes in shape of the distribution curve during the desorption process.

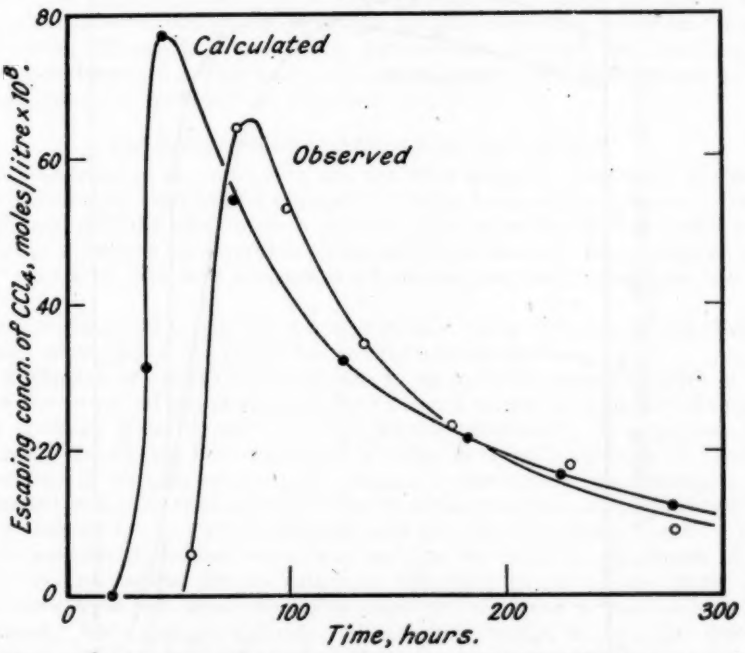
The Concentration of Gas in the Effluent Stream during Desorption.

When the adsorbed gas reaches the end of the column it will pass into the effluent stream. In general, there is an initial period during which no gas can be detected in the effluent; the concentration then rises rapidly to a maximum and finally decreases slowly in a more or less exponential manner.

We have seen that for practical purposes adsorption equilibrium is maintained during desorption in systems of the type we are considering. The concentration of gas in the effluent stream at any instant will therefore correspond to equilibrium with that adsorbed on the final layer of the column and may be calculated by the methods described in the last section.

In Figs. 11 and 12 are shown the observed and the calculated curves for the variation in effluent concentration with time during desorption from columns previously treated with carbon tetrachloride and with water. The agreement is close. For reasons already discussed, water vapour penetrates through the column, even in the brief initial treatment. This leads to a high concentration of water vapour in the effluent stream at the beginning of the desorption.

FIG. 11.



Variation with time of the effluent concentration of carbon tetrachloride during desorption.

Similar calculations have been made for hydrogen cyanide and cyanogen chloride. As already explained, the former reacts slowly on charcoal to give products which are not desorbed. As would be expected, therefore, the amount of hydrogen cyanide actually desorbed from a column is appreciably less than that calculated. The form of the calculated curve is, however, in general agreement with experiment. The same considerations, in general, apply to cyanogen chloride.

The Later Stages of Desorption.

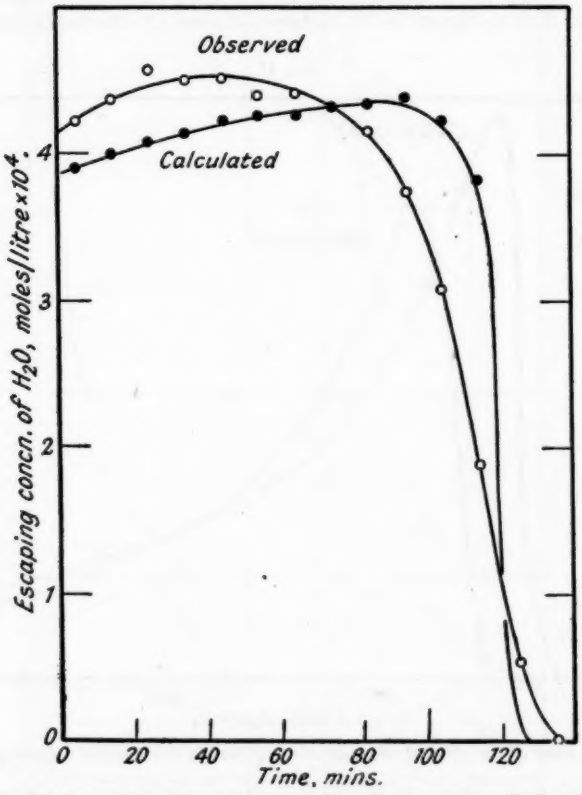
During desorption the point of maximum adsorbed concentration moves through the column. The arrival of this maximum at the end of the column corresponds to the maximum concentration of gas in the effluent stream. The concentration of adsorbed gas is by this time fairly uniform along the column. The process of desorption would thereafter be expected to resemble that from homogeneously saturated charcoal in an adsorption balance.

Experiments with such a balance have shown that the behaviour of different gases on desorption conforms to one of three main types. These are exemplified severally by carbon tetrachloride, water, and hydrogen cyanide, and may be related directly to the adsorption

isotherms. The idealisation of charcoal columns by the very small quantities of charcoal used in an experiment with an adsorption balance may constitute an over simplification, but for our purpose the two sets of conditions are sufficiently comparable.

The desorption of carbon tetrachloride is characterised by a linear decrease in the amount retained with the *logarithm of the time* of desorption. This means that there is a very rapid decrease in desorption rate with decreasing amounts of material remaining adsorbed. In practice the rate of desorption may become almost negligible while the amount adsorbed is still appreciable. The desorption of carbon tetrachloride from a column must, at least qualitatively, follow such a course. For example, in the experiment from which the results given in Fig. 11 were derived, the vapour originally admitted was completely adsorbed within the first 1·5 cm. of the column. On passage of air, 18 hours elapsed before carbon tetrachloride escaped from the

FIG. 12.



Variation with time of the effluent concentration of water vapour during desorption.

end of the 6-cm. column. After 65 hours' desorption, the mean concentration on the final layers of the column was 13·43% by weight; after 89 hours it had fallen only to 12·27%. During the intervening period of 24 hours the total amount of carbon tetrachloride desorbed from the entire column was only 28·1 mg. In the air stream of 200 c.c./min. this corresponds to a dilution of about 10^5. Though this would appear to be a remarkably low rate of desorption from a completely penetrated column, it will be seen that it is to be expected from a consideration of the form of the desorption curve and isotherm. The two operative factors are the high maximum adsorption and the very rapid fall in the desorption rate with decreasing amount adsorbed, the latter being inherent in the linear relation between amount adsorbed and the logarithm of the time.

A sharp contrast with the behaviour of carbon tetrachloride is shown by that of water. Here there is a nearly linear relation between the amount remaining adsorbed and the time (in contrast with the *logarithm* of the time with carbon tetrachloride). This means that the rate of desorption is nearly constant over a considerable range, and decreases only when the amount

remaining adsorbed is very small. We should therefore expect that in the desorption of water vapour the concentration in the effluent would first remain constant, and then fall very rapidly. As will be seen from Fig. 12, this situation is completely realised. The practical significance of this type of behaviour is obvious. Substances, such as water, having S-shaped adsorption isotherms, will be desorbed very readily.

Hydrogen cyanide shows an intermediate type of behaviour. The rate of desorption is approximately proportional to the amount remaining adsorbed. In a constant air stream the latter will therefore decrease in a more or less exponential manner. The falling branch of the experimental curves for the effluent hydrogen cyanide concentration are found to be of this type. The behaviour of cyanogen chloride is rather similar, though at lower pressures it becomes intermediate in character between hydrogen cyanide and carbon tetrachloride. This again is expected from its adsorption isotherm.

The close relation between the form of the desorption curves of the different substances and their adsorption isotherms is very clear. The nearly constant desorption rate of water depends essentially on the fact that, according to its isotherm, the vapour pressure over the adsorbent changes little over wide ranges of the amount adsorbed. The hydrogen cyanide isotherm is roughly linear: the vapour pressure over the charcoal, and hence the desorption rate is therefore proportional to the amount of hydrogen cyanide remaining adsorbed. Finally, with carbon tetrachloride, the vapour pressure over the surface falls more and more rapidly as the amount adsorbed is decreased. This leads to vanishingly small desorption rates from charcoal still containing appreciable quantities of adsorbed vapour.

The Redistribution of Adsorbed Gas by Diffusion.

After a brief treatment of a column with gas, the latter is largely confined to the initial layers. We have now to consider distribution changes resulting from simple diffusion when no air is passed through, and also the effect of such redistribution on subsequent desorption into an air stream. This has a bearing on several practical problems (such as the storage of a respirator after a short period of use in a contaminated atmosphere and subsequent use on a later occasion).

A rigorous mathematical treatment is impracticable. The diffusion of adsorbed gas along the column may, however, be calculated by an approximate method.

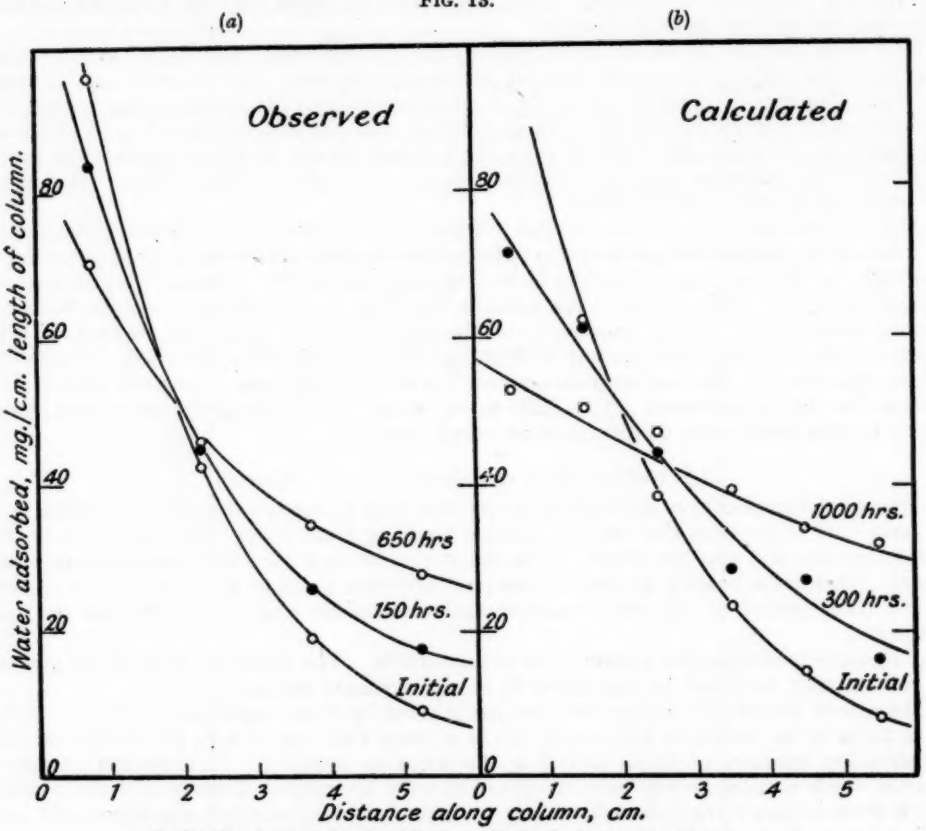
The rate of diffusion of one gas into another is given by Fick's equation $dw/dt = -D.dc/dl$, where dw/dt is the weight of gas passing across a plane 1 sq. cm. in area per second through a concentration gradient of dc/dl, and D is the diffusion constant. In a packed column the distance which a molecule will have to diffuse in order to travel a distance of 1 cm. along the tube is greater than if the tube were empty. Similarly, the concentration gradient will be less along this extended path than that measured directly along the tube. To a rough approximation the path may be assumed to be 1·5 times as great, and the concentration gradient correspondingly less. These corrections have been taken into account by suitable adjustment of the values taken for D. Precise values for the diffusion constants in air of the gases used in the experimental work were not available. The value 0·1 cm.^{2} sec.$^{-1}$ was used for water and hydrogen cyanide. For cyanogen chloride and carbon tetrachloride the value 0·05 cm.^{2} sec.$^{-1}$ has been assumed. The cross-section area of the gas space in a packed column has been taken as 0·25 of that of the tube.

In the calculations of diffusion a differential method similar to that used in the preceding sections has been applied. Gas is assumed to be admitted to the column (its distribution being known by experiment or calculation), and from the isotherm the partial pressure over each element of the column is obtained. This gives the concentration gradient at all points. Diffusion is then allowed to take place for a given time interval, and the amount of gas which would diffuse from each element to the next is calculated from Fick's equation in its differential form. Adsorption equilibrium is assumed to be attained and the method of successive approximation used to obtain the amount of gas adsorbed on each element and the partial pressure over it. The concentration gradients corresponding to this new distribution are then calculated, and the process repeated for another interval of time. In this way we obtain a series of curves giving an approximate picture of the progressive diffusion of the adsorbed gas along the column.

Calculations by this method showed that redistribution of adsorbed hydrogen cyanide, water, cyanogen chloride, and carbon tetrachloride by diffusion alone would be expected to take place at about one fiftieth to one hundredth of the rate caused by the standard air stream previously considered.

The redistribution of adsorbed water by diffusion has been investigated experimentally by methods already described. The results are given in Fig. 13(*a*). Good agreement is shown with the calculated values in Fig. 13(*b*).

FIG. 13.



Redistribution by simple diffusion of adsorbed water vapour.

This paper is published with the approval of the Director General of Scientific Research (Defence), Ministry of Supply, to whom thanks are expressed.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, July 5th*, 1946.]

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83. *The Interchange of Heat between a Gas Stream and Solid Granules. Part I.*

By J. R. ARTHUR and J. W. LINNETT.

The temperature distribution in a bed of charcoal granules through which air is streaming and to which heat is being supplied by a heater embedded in the charcoal has been studied. The plot of the logarithm of the temperature at the steady state against the distance down the column gives two straight lines, one for the region on the near side of the heater and the second for the region on the far side. The slope of the log $T-x$ graph is dependent on the flow rate but independent of the rate at which heat is supplied by the heater. A mathematical treatment is described which accounts precisely for the results obtained. According to this treatment the rate of interchange of heat between the gas and the solid is proportional to the temperature difference between them. Moreover, the rate of interchange of heat is rapid compared with the conduction of heat through the charcoal, so it is concluded that, at the steady state, the temperature of the air follows closely the charcoal temperature at all points in the system examined.

GILBERT (*Engineer*, 1930, **150**, 500, 530, 574, 617, 640) and Furnas (*Ind. Eng. Chem.*, 1930, **22**, 26, 721) have studied the passage of heat between a gas stream and a bed of granules maintained

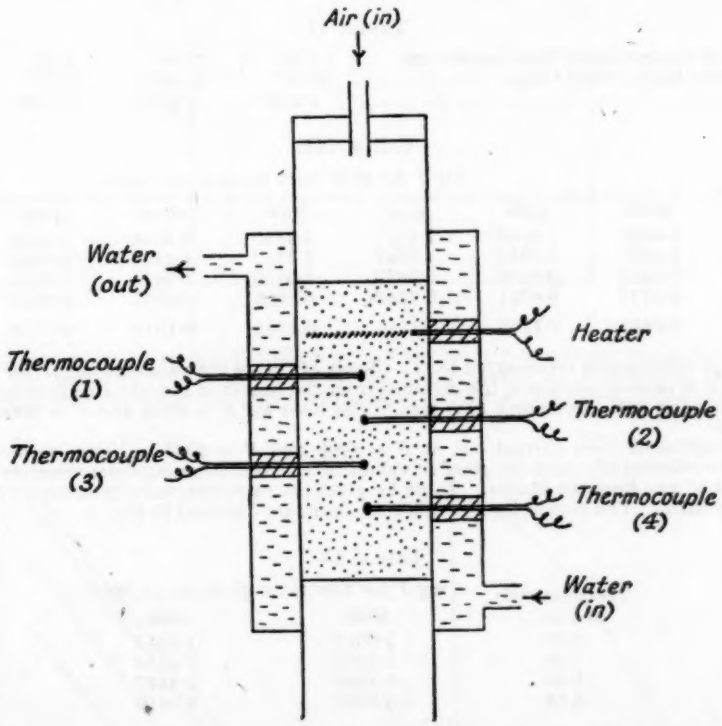
at different temperatures. We studied the passage of heat between an air stream and a bed of charcoal granules in a system which was constructed to resemble a catalytic system. In the latter, heat is produced by a chemical reaction over a volume of the granular bed, while in our idealised arrangement heat was produced electically at a given layer. Results obtained for a real catalytic system will be published later.

Experimental.

The charcoal granules used to make the granular bed were graded between 8 and 18 B.S.S. and were dried by heating to 120°. The air used was dried with calcium chloride and concentrated sulphuric acid. The granular bed was contained in a metal tube, 29·7 cm. long and of 4·7 cm. internal diameter. The tube was set vertically and water-jacketed so that the wall temperature remained constant. The tube was fitted with short side tubes at intervals of 1·5 cm. down its length through which passed the leads to the heating element and the thermocouples that measured the temperature of the granules (see Fig. 1).

The heating element was a wire grid on a square glass frame of side 2·5 cm. The wire was 33 S.W.G. constantan. Its resistance was about 3 ohms. The current, supplied by two 2-volt accumulators, was

Fig. 1.



kept constant with a variable resistance and measured in arbitrary units on an ammeter. The heating element was placed perpendicular to the axis of the tube, and the leads passed out through a rubber stopper in a side tube. The inner part of the stopper was flush with the tube wall. Copper–constantan thermocouples were used. In a preliminary experiment the effect of the diameter of the wires forming the thermocouple was investigated. The temperatures recorded by three thermocouples at a constant bed temperature are shown in Table I. The recorded temperature varies approximately linearly with the area of the wires. Since the area of the two 40 S.W.G. wires is very small, it may be presumed that a thermocouple made from these records fairly well the temperature of the charcoal at the junction.

Table I.

Wires used in thermo-couple.	100 × total area of two wires, sq. mm.	Temp. recorded by thermocouple.
28 S.W.G. Constantan 24 S.W.G. Copper	27·16	33·3°
33 S.W.G. Constantan 32 S.W.G. Copper	11·06	40·1
40 S.W.G. Constantan 40 S.W.G. Copper	2·26	44·8

The error is probably less than 1°. The junction between the two wires was made in a sphere of solder about the size of a charcoal granule. The two wires were led in through fine glass tubes which passed through a rubber stopper. The cold junctions were kept at 0°. In a single experiment four thermocouples were used. These were calibrated by placing their hot junctions in steam, all giving $0{\cdot}4286 \pm 0{\cdot}0003 \times 10^{-3}$ volt. The E.M.F.'s were measured on a Tinsley general utility potentiometer standardised against a Weston cadmium cell. It is presumed in what follows that the thermocouples measure the charcoal temperature since the sphere of solder at the junction resembled a granule of charcoal. The air flow rate through the bed, measured on a capillary flowmeter, could be varied between 2000 and 5000 c.c./min.

(1) In the first set of experiments four thermo-junctions were located along the axis of the charcoal column on the side of the heating element remote from the air inlet. The charcoal column was 11·3 cm. long, and the heating element 1·05 cm. from the top. The junctions were placed 1·40, 2·65, 4·50 and 5·85 cm. from the element. The E.M.F. of each junction was read every two minutes. When the charcoal temperature was steady and uniform the air was turned on and the final steady temperature of each junction recorded. This was carried out for flow rates (F) of 2000, 2500, 3000, 3500, 4000, 4500, and 5000 c.c./min. The following tables give only the final steady temperature, and the mathematical treatment is of the steady state and not of the approach to that state.

Table II gives the differences between the steady temperatures recorded by the thermocouples and the wall temperature (which was 13¼°) for an experiment carried out with a flow rate of 3500 c.c./min.

TABLE II.

Distance of thermocouple from heater, cm. ...	1·40	2·65	4·50	5·85
Final steady temp.—wall temp.	28·50°	18·98°	10·37°	6·63°
$\log_{10} T$	1·4549	1·2783	1·0156	0·8215

TABLE III.

Thermocouple at (cm.).	log T for flow rates given in c.c./min.						
	2000.	2500.	3000.	3500.	4000.	4500.	5000.
1·40	1·4427	1·4549	1·4517	1·4549	1·4448	1·4293	1·4244
2·65	1·2007	1·2386	1·2547	1·2783	1·2852	1·2825	1·2873
4·50	0·8424	0·9160	0·9637	1·0156	1·0431	1·0548	1·0800
5·85	0·5777	0·6761	0·7466	0·8215	0·8665	0·8932	0·9160
Slope of line	0·1948	0·1768	0·1584	0·1444	0·1314	0·1218	0·1128

The temperature difference is represented by T. Table III gives the values of $\log_{10}T$ for the seven flow rates. If $\log_{10}T$ is plotted against x, the distance from the heater, a straight line is obtained, the slope of the line increasing with decreasing flow rate. The lines for $F = 2000$ and $F = 5000$ c.c./min. are shown in Fig. 2.

Further experiments were carried out at $F = 4000$ and $F = 5000$ c.c./min. to see whether this important linear relationship held for smaller values of x. The thermocouples were on the axis 0·20, 1·20, 1·45 and 4·55 cm. from the heater. Table IV gives the experimentally determined values of log T for the two flow rates. The results for $F = 5000$ c.c./min. are included in Fig. 2.

TABLE IV.

Thermocouple at (cm.).	log T for flow rates given in c.c./min.	
	4000.	5000.
0·20	1·6077	1·5514
1·20	1·4881	1·4564
1·45	1·4293	1·4147
4·55	0·9925	1·0619

The slopes of the $\log_{10}T$–x lines are given in the last row of Table III. It is found empirically that the reciprocal of the slope varies linearly with the flow rate.

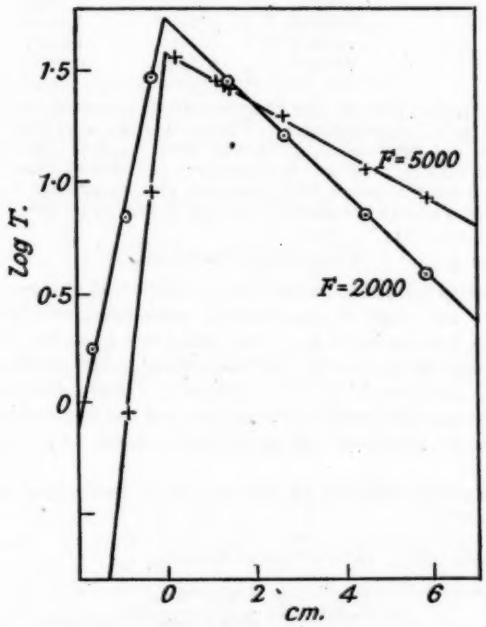
(2) A second series of measurements was made with thermocouples on the axis of the tube on the side of the heater adjacent to the incoming air. They were 0·30, 0·90, 1·70, and 2·85 cm. from the heater, but the junction at 2·85 cm. never showed any appreciable heating. Except at the lowest flow rate the temperature at 1·70 cm. from the heater was raised less than 1° so the percentage error in this reading was quite high. The values of $\log_{10}T$ at the steady state are shown in Table V for flow rates between 2000 and 5000 c.c./min. If the temperature at $x = 0$, obtained by extrapolating the results listed in Table III for temperatures beyond the heater, is used in conjunction with the figures in Table V it is found that,

TABLE V.

Thermocouple at (cm.).	log T for flow rates given in c.c./min.						
	2000.	2500.	3000.	3500.	4000.	4500.	5000.
0·30	1·4658	1·3988	1·3413	1·2564	1·1917	1·1264	0·9503
0·90	0·8336	0·6945	0·5696	0·3976	0·2925	0·1164	−0·0407
1·70	0·2433	−0·0407	−0·1694	−0·4277	−0·4557	−0·7287	−0·4857
Slope of line	0·950	1·101	1·202	1·387	1·474	1·620	1·718

for negative values of x also, log T varies linearly with x. Fig. 2 shows the graphs for $F = 2000$ and 5000 c.c./min. The slopes of the lines are given in Table V. It is found empirically that the slope varies linearly with the flow rate.

FIG. 2.



(3) In a third set of measurements the effect of varying the current through the heater was examined. Measurements were made with currents of 20, 24, 28, and 30 units, 28 units having been used in the first and second series. The thermocouples were placed as in the first series and a flow rate of 4000

FIG. 3.

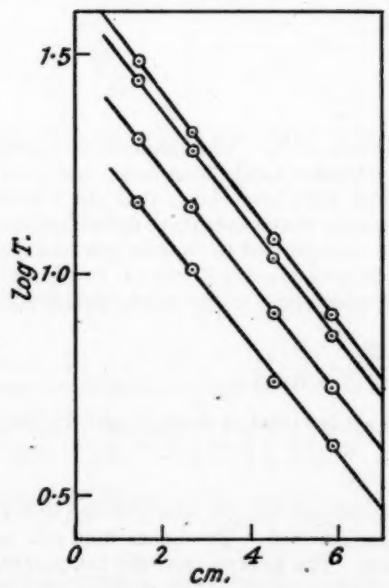
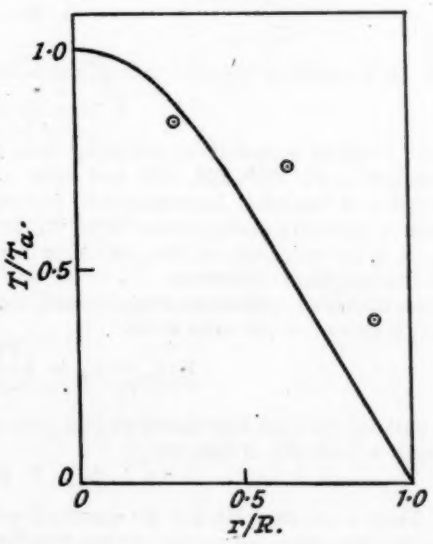


FIG. 4.



c.c./min. was used. The results are listed in Table VI and shown graphically in Fig. 3. It will be seen that the slope of the $\log_{10}T$–x plot is independent of the rate at which heat is produced by the element, being dependent, for a given bed, only on the air-flow rate.

TABLE VI.

Thermocouple at (cm.).	log T for different heating currents ($F = 4000$). Units: 20.	24.	28.	30.
1·40	1·1648	1·3117	1·4448	1·4871
2·65	1·0146	1·1578	1·2852	1·3287
4·50	0·7661	0·9196	1·0431	1·0850
5·85	0·6162	0·7484	0·8665	0·9123

(4) In a fourth series of measurements the temperature distribution across the column at a given depth (4·3 cm. beyond the heater) was examined. Thermocouples were placed 0·0, 0·7, 1·5, and 2·1 cm. from the axis, and flow rates of 2000, 3000, 4000, and 5000 c.c./min. were used. It was found that T/T_a (T_a is the temperature on the axis) was independent of the flow rate, being 1·00, 0·83, 0·73, and 0·38 at the above distances from the axis. The ratios are plotted against the distance from the axis in Fig. 4, and on the same figure is drawn the Bessel function of zero order (see " Theoretical Treatment ").

Theoretical Treatment.

In the above experiments air passed through a cylindrical column of charcoal. The walls of the tube, and therefore the edge of the column, were kept at a steady temperature. Let distances down the column be measured as x, and distances from the axis as r. Let the heater supplying heat to the column be at $x = 0$. We will examine the conditions in a ring of charcoal of radius r, thickness dr, and depth dx at a distance x from the heater. In the following treatment the expansion of the air flowing through the bed has been ignored. Since the absolute temperature of the air never increased by more than about 15% this omission is probably justifiable.

The heat gained and lost by the ring of charcoal may be represented as made up of three parts:

(i) By conduction horizontally; rate of loss of heat is

$$-k \cdot 2\pi r \cdot dx \frac{1}{r}\frac{d}{dr}\left(r\frac{dT_c}{dr}\right)dr$$

where k is the thermal conductivity of the granular bed of charcoal and T_c is the charcoal temperature, measured from the wall temperature which is taken as our zero.

(ii) By conduction vertically; rate of loss of heat is

$$-k \cdot 2\pi r \cdot dr \frac{d^2T_c}{dx^2}dx$$

(iii) By transfer to the air; rate of loss of heat is

$$K \cdot 2\pi r \cdot dr \cdot dx(T_c - T_g)$$

where T_g is the air temperature measured from the same zero as T_c. This assumes, as Schumann (*J. Franklin Inst.*, 1929, **208**, 405) and other workers (Walker, Lewis, McAdams, and Gilliland, " Principles of Chemical Engineering ", McGraw-Hill, p. 107) have done, that the transfer of heat from a solid to a gas in contact with it is proportional to the temperature difference between them; K is the constant for this heat interchange and is expressed in calories per unit volume per unit temperature difference.

When the steady state has been reached, the rate at which heat is lost must equal the rate at which it is gained, so we may write:

$$K(T_c - T_g) = k\left[\frac{1}{r}\frac{d}{dr}\left(r\frac{dT_c}{dr}\right) + \frac{d^2T_c}{dx^2}\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

In passing through the above ring of charcoal the air is raised in temperature by dT_g and this requires a supply of heat of

$$dT_g \cdot S \cdot 2\pi r \cdot dr \cdot L\rho$$

where S and ρ are respectively the specific heat and density of the gas, and L is the linear flow rate in the free tube before the stream reaches the charcoal bed. The linear flow rate in the bed is L divided by the fractional free space in the bed. The heat to raise the temperature of the air is supplied in two ways:

(*a*) From the charcoal:

$$K \cdot 2\pi r \cdot dr \cdot dx(T_c - T_g)$$

(*b*) Because of cross channels between the granules, parts of the air stream will, at times, move laterally while flowing through the bed. This will result in a horizontal transfer of heat by convection, which will be given by a term of the form

$$C \cdot 2\pi r \cdot \mathrm{d}x \frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_g}{\mathrm{d}r}\right)\mathrm{d}r$$

For the steady state, since there is no change with time, we have

$$\frac{\mathrm{d}T_g}{\mathrm{d}x} = \frac{K}{\rho SL}(T_c - T_g) + \frac{C}{\rho SL}\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_g}{\mathrm{d}r}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Let $\Delta T = T_c - T_g$; then equation (2) can be written as

$$\frac{\mathrm{d}T_c}{\mathrm{d}x} - \frac{\mathrm{d}(\Delta T)}{\mathrm{d}x} - \frac{K}{\rho SL}(\Delta T) - \frac{C}{\rho SL}\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_c}{\mathrm{d}r}\right) + \frac{C}{\rho SL}\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}(\Delta T)}{\mathrm{d}r}\right) = 0$$

Substitution in this of (ΔT) from equation (1) gives

$$\frac{\mathrm{d}^3T_c}{\mathrm{d}x^3} + \frac{K}{\rho SL}\cdot\frac{\mathrm{d}^2T_c}{\mathrm{d}x^2} - \frac{K}{k}\cdot\frac{\mathrm{d}T_c}{\mathrm{d}x} + \frac{\mathrm{d}}{\mathrm{d}x}\cdot\frac{1}{r}\cdot\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_c}{\mathrm{d}r}\right) + \frac{K}{\rho SL}\cdot\frac{1}{r}\cdot\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_c}{\mathrm{d}r}\right)$$
$$+ \frac{C}{\rho SL}\frac{K}{k}\left[\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}T_c}{\mathrm{d}r}\right) - \frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}(\Delta T)}{\mathrm{d}r}\right)\right] = 0 \quad . \quad . \quad (3)$$

It will be seen later that, to explain the experimental results, K has to be assumed to be large; *i.e.*, the air temperature follows the charcoal temperature very closely through the column and (ΔT) is always very small. Therefore the last term in equation (3) may be neglected. This has been tested and found to be justified.

Let it be supposed that, to a first approximation, we may represent $T_c(x, r)$ as the product of a part dependent on x only and a part dependent on r only; *i.e.*,

$$T_c(x, r) = T_c^*(x) \cdot \mathrm{f}(r) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

It is supposed that T_c^* is the temperature of the charcoal on the axis of the tube and that $\mathrm{f}(r)$ varies from unity at $r = 0$ to zero at the outside edge of the charcoal ($r = R$). Substitution of (4) into (3) gives

$$\frac{\mathrm{d}^3T_c^*}{\mathrm{d}x^3} + \frac{K}{\rho SL}\frac{\mathrm{d}^2T_c^*}{\mathrm{d}x^2} - \left[\frac{K}{k} - \frac{\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}(r\mathrm{f}'(r))}{\mathrm{f}(r)}\right]\frac{\mathrm{d}T_c^*}{\mathrm{d}x} + \left[\frac{C+k}{k}\right]\frac{K}{\rho SL}\cdot\frac{\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}(r\mathrm{f}'(r))}{\mathrm{f}(r)}T_c^* = 0 \quad . \quad (5)$$

For equation (5) to hold and (4) to be true we must have:

$$\frac{\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}(r\mathrm{f}'(r))}{\mathrm{f}(r)} = \text{a constant } (A) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The solution of (6) which satisfies the boundary conditions, $\mathrm{f}(0) = 1$ and $\mathrm{f}(R) = 0$, is the Bessel function of zero order, $\mathrm{J}_0(y)$, where $y = -\sqrt{A}.r$. Since $\mathrm{J}_0(y) = 0$ when $y = 2{\cdot}405$,

$$A = -(2{\cdot}405/R)^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

This can be substituted back into (5) to give the following equation:

$$\frac{\mathrm{d}^3T_c^*}{\mathrm{d}x^3} + \frac{K}{\rho SL}\cdot\frac{\mathrm{d}^2T_c^*}{\mathrm{d}x^2} - \left[\frac{K}{k} + \left(\frac{2{\cdot}405}{R}\right)^2\right]\frac{\mathrm{d}T_c^*}{\mathrm{d}x} - \left[\frac{C+k}{k}\right]\frac{K}{\rho SL}\left(\frac{2{\cdot}405}{R}\right)^2 T_c^* = 0 \quad . \quad (5a)$$

The general solution of this equation is

$$T_c^*(x) = \Sigma a e^{mx} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

where the values of m are solutions of the cubic equation

$$m^3 + \frac{K}{\rho SL}m^2 - \left[\frac{K}{k} + \left(\frac{2{\cdot}405}{R}\right)^2\right]m - \left[\frac{C+k}{k}\right]\frac{K}{\rho SL}\left(\frac{2{\cdot}405}{R}\right)^2 = 0 \quad . \quad . \quad (9)$$

It is found that there is one positive root (m_1) and two negative roots (m_2 and m_3). Since T_c^* must become zero when x goes to either plus or minus infinity, we must have:

$$\text{For } x < 0 \qquad T_c^* = a_1 e^{m_1 x}$$

$$\text{For } x > 0 \qquad T_c^* = a_2 e^{m_2 x} + a_3 e^{m_3 x}$$

Substituting in equation (1), we obtain:

$$\text{For } x < 0 \qquad \Delta T^* = b_1 e^{m_1 x}$$

$$\text{For } x > 0 \qquad \Delta T^* = b_2 e^{m_2 x} + b_3 e^{m_3 x}$$

The b values can be calculated from the a and m values by using equation (1); a_2 and a_3 can be calculated in terms of a_1 by using the condition that at $x = 0$, T_c^* and (ΔT^*) must be single valued. That is, the equations that give their values on each side of zero must lead, at zero, to the same value; a_1 can then be fixed to give the curve appropriate to the particular heating current used.

Numerical Calculations.—In Fig. 4 the experimentally determined temperature distribution across the tube was compared with the appropriate Bessel function distribution. Because the distances involved were small (four thermocouples in a distance of 2 cm.) we consider that the experimentally determined distribution across the tube was as close as could be expected to that deduced theoretically from equation (7).

The experiments were carried out in a tube having $R = 2{\cdot}35$ cm., which gives $A = -1{\cdot}047S\rho$; the number of calories required to heat 1 c.c. of gas through 1° at constant pressure is taken as $3{\cdot}125 \times 10^{-4}$. The relation between L, the linear flow rate, and F, the volume flow rate, is $1041L = F$, if F is expressed in c.c./min. and L in cm. per second. For example, $F = 5000$ c.c./min. corresponds to $L = 4{\cdot}804$ cm./sec. The values of k and K are not known for the particular bed of charcoal used, so they are taken to give the best fit to the experimental results. The values used are:

$k = 3{\cdot}2 \times 10^{-4}$ cal. per sq. cm. per sec. per unit temperature gradient;

$K = 2{\cdot}1 \times 10^{-3}$ cal. per c.c. per sec. per unit temperature difference.

The value of C, over the range of flow rates used, was obtained from the purely empirical formula

$$C \times 10^4 = 0{\cdot}23(F/1000) - 0{\cdot}325 = 0{\cdot}24L - 0{\cdot}325$$

This gives values of C increasing as the flow rate increases. This would be expected, since movement in the cross channels would be expected to increase with increasing flow rate. This will make the lateral transfer of heat greater.

The values of m for the different flow rates are obtained by solving the cubic equation (9). The values of a_2/a_1 and a_3/a_1 are obtained by applying the boundary condition that T_c^* and (ΔT^*) shall be single valued at $x = 0$. Equation (1) then gives values of b_1, b_2, and b_3 relative to a_1. The results are shown in Table VII.

TABLE VII.

F.	$C \times 10^4$.	m_1.	m_2.	m_3.	a_2/a_1.	a_3/a_1.	b_1/a_1.	b_3/a_1.
2000	0·135	2·244	−36·74	−0·4618	0·0036	0·9964	0·0608	−0·0127
2500	0·250	2·582	−30·15	−0·4056	0·0072	0·9928	0·0856	−0·0134
3000	0·365	2·901	−25·85	−0·3627	0·0124	0·9876	0·1123	−0·0138
3500	0·480	3·201	−22·85	−0·3291	0·0194	0·9806	0·1402	−0·0140
4000	0·595	3·478	−20·67	−0·3023	0·0281	0·9719	0·1683	−0·0142
4500	0·710	3·737	−19·00	−0·2803	0·0385	0·9615	0·1967	−0·0142
5000	0·825	3·970	−17·69	−0·2621	0·0502	0·9498	0·2384	−0·0142

The theory predicts that the temperature falls off exponentially on the near side of the heater ($x < 0$). For $x > 0$, the temperature is the sum of two exponential terms; but, since m_2 has a large negative value and a_2 is small, this term is never big and becomes quite negligible when x is still quite small. So, to a very close approximation:

$$\text{For } x > ca.\ 0{\cdot}1 \text{ cm.}, \qquad T_c^* = a_3 e^{m_3 x}$$

Therefore our theory predicts that the temperature falls off exponentially on the far side of the heater, except when x is very small. The value of m_3, for a given charcoal bed, depends only on the flow rate and is predicted to be independent of the rate of heat supply. This was found experimentally (see Table IV and Fig. 3).

In the experimental section the results were shown graphically in the form :

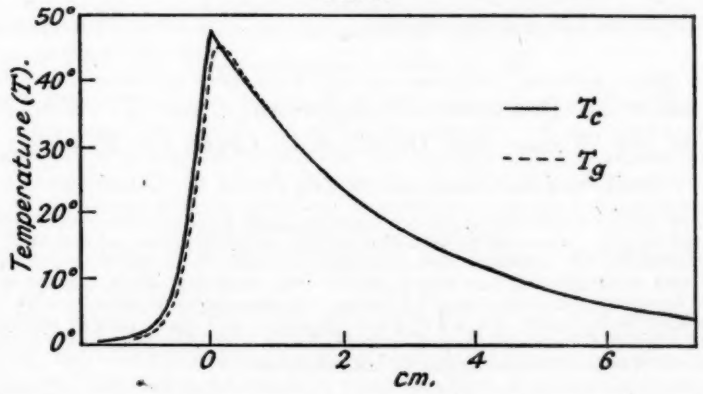
$$\text{For } x < 0, \qquad \log_{10}T = X + m_1'x$$
$$\text{For } x > ca.\ 0{\cdot}1 \text{ cm.}, \qquad \log_{10}T = Y + m_3'x$$

X and Y were assumed identical. On the present theory, X and Y differ slightly (always less than 2%). The values of m_1' and m_3' obtained theoretically (from m_1 and m_3 in Table VII) are compared in Table VIII with the experimental values. The value of Y is chosen to give the best fit with the experimental results, and from this and a_2/a_1, $(Y - X)$ is calculated. The calculated and experimental m' values are seen to agree well. In Fig. 2 the agreement is shown

TABLE VIII.

Flow rate in c.c./min.	m_1'. calc.	m_1'. obs.	m_3'. calc.	m_3'. obs.	Y.	$(Y - X)$.
2000	0·974	0·950	−0·2005	−0·1948	1·364	0·0015
2500	1·121	1·101	−0·1762	−0·1768	1·337	0·0032
3000	1·260	1·202	−0·1575	−0·1584	1·304	0·0054
3500	1·390	1·387	−0·1429	−0·1444	1·289	0·0085
4000	1·510	1·474	−0·1313	−0·1314	1·264	0·0124
4500	1·623	1·620	−0·1218	−0·1218	1·233	0·0171
5000	1·724	1·718	−0·1138	−0·1128	1·209	0·0223

FIG. 5.



graphically where, for $F = 2000$ and 5000 c.c./min., the graph is that theoretically deduced. The points are experimental.

The above theory was developed for an infinite layer, whereas the experiments were carried out on a finite layer. However, because the temperature falls off rapidly on the near side of the heater, the temperature at the top of the column is nearly equal to that of the wall and incoming gas ($T = 0$), so very little difference may be expected between the behaviour of the finite and an infinite column.

Discussion.

The agreement between theory and experiment shown in Table VIII suggests that the theory gives an accurate picture of the thermal conditions in the charcoal bed. It is important to compare the present theory with others. One important assumption made here was that the heat interchange between gas and solid was proportional to the temperature difference between them. The results suggest that this is valid. It was assumed by Schumann in his treatment, and Furnas's results supported Schumann's assumption. Also, results for heat transfer between the walls of a tube and the gas flowing through it have been satisfactorily explained by a similar assumption.

The value of the constant K, for this heat interchange, was required to be 0·023. Furnas gives values of this constant as it depends on granule size. Because his granules were larger than ours he obtained, in the main, rather smaller values of K, namely, *ca.* 0·01. However, the two values are of the same order of magnitude. Moreover, the value we used is very much what would be expected if Furnas's results are extrapolated to granules of the size we used.

The value assumed for k, the thermal conductivity, was 0·00032. This is of the correct order of magnitude for the thermal conductivity of such a bed of granules (see, *e.g.*, the work of Ingersoll and Koepp, *Physical Rev.*, 1924, **24**, 92). In the International Critical Tables the thermal conductivity of coke dust is given as 0·0004 and that of charcoal as 0·00014. So the value we found it necessary to assume is reasonable.

The fact that K, the constant for heat interchange, is much greater than k, the thermal conductivity, means that, when the steady state is reached, the air temperature is very close to the charcoal temperature throughout the column. In Fig. 5, T_c^* and T_g^* down the axis of the charcoal are plotted for $F = 3500$ c.c./min. The difference between them is small at all points.

Previous workers studying the interchange of heat between a solid and a gas flowing over it have considered that the rate of heat interchange depends on the gas velocity (Walker, Lewis, McAdams, and Gilliland, *op. cit.*, p. 109). We have taken K to be independent of the flow rate. This distinguishes our treatment from those of other workers. However, we have taken lateral movement of air in the bed into account (the term involving C). It has been necessary to make the reasonable supposition that C is dependent on the flow rate. So the condition of heat passage to and fro does depend on the flow rate. If the term involving C had been omitted from the theoretical treatment, it would have been necessary to assume that K was dependent on the flow rate. However, our results have been successfully accounted for by the much more reasonable assumption of a constant K and a lateral movement of air within the bed, which must certainly take place; this lateral movement depending on the flow rate.

We wish to thank the Director General of Scientific Research (Defence), Ministry of Supply, for giving us permission to publish this work.

INORGANIC CHEMISTRY LABORATORY, OXFORD. [*Received, July 9th*, 1946.]

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84. *Studies on Biological Methylation. Part X. The Fission of the Mono- and Di-sulphide Links by Moulds.*

By FREDERICK CHALLENGER and PHILIP T. CHARLTON.

The fungus *Schizophyllum commune* converts inorganic sulphate into methylthiol (Birkinshaw *et al.*, see below). The authors have detected dimethyl sulphide and dimethyl disulphide among the products. *S. commune* forms dimethyl selenide in presence of sodium selenate. Methylthiol and dimethyl sulphide are produced from dimethyl disulphide by the fungus. Diethyl and di-*n*-propyl disulphides yield thiols. *Scopulariopsis brevicaulis* with methionine and the *S*-alkylcysteines (Me, Et, *n*-Pr) gives alkylthiol and alkyl methyl sulphides. This fission of the Alkyl-S–C link appears to be a new type of microbiological action which presents analogy with the fission of cystathionine in animal tissues.

IT was shown by one of us with Rawlings (*J.*, 1937, 868) and Blackburn (*J.*, 1938, 1872) that bread cultures of *Scopulariopsis brevicaulis* cause fission of the –S–S– link of disulphides, R·S·S·R, (R = methyl to *n*-amyl) giving the thiol, R·SH, and the alkyl methyl sulphide, R·SMe. Inorganic sulphates are unaffected by *S. brevicaulis*, but Birkinshaw, Findlay, and Webb (*Biochem. J.*, 1942, **36**, 526) showed that the wood-destroying fungus *Schizophyllum commune* when grown on a medium containing glucose and inorganic sulphate evolves methylthiol and traces of hydrogen sulphide. This is the first recorded instance of the methylation of inorganic sulphur by a microbiological process. Mr. Findlay kindly sent us a culture of this organism. Cultures on wort, and especially on bread, without added substrate evolved methylthiol, due to combined sulphur in the medium. When the cultures were almost odourless other substrates were added. Sodium selenate gave dimethyl selenide in small quantity. Potassium tellurite gave black tellurium, and the odour of dimethyl telluride could hardly be detected. Arsenious oxide, and methylarsonic, cacodylic, and *n*-propylarsonic acids gave no more than a very faint garlic odour. *S. commune* therefore appears to have a weaker methylating action than *S. brevicaulis*.

Birkinshaw *et al.* do not mention the production of dimethyl sulphide by *S. commune*, but we find that this is evolved in small quantities with some dimethyl disulphide, probably arising from oxidation of methylthiol. Absorption in mercuric chloride, after removal of methylthiol by mercuric cyanide, gives a mixture of dimethyl sulphide mercurichloride, $2Me_2S,3HgCl_2$, and methylthiomercuric chloride, MeSHgCl, or its mercurichloride $MeSHgCl,xHgCl_2$. The first compound yields dimethyl sulphide with sodium hydroxide. The other two, which arise from the disulphide by fission (*J.*, 1938, 1872, 1878), evolve no sulphur compound under these conditions.

The concentrated culture medium contained traces of pyruvic acid.

The dimethyl sulphide might be produced by a mechanism analogous to that suggested by one of us (*Chem. and Ind.*, 1942, **61**, 414; *Chem. Reviews*, 1945, **36**, 343) to explain the formation of dimethyl selenide from sodium selenate, thus: $Na_2SO_4 \longrightarrow Na_2SO_3 \longrightarrow MeSO_2 \cdot ONa \longrightarrow Me \cdot SO_2Na \longrightarrow Me_2SO_2 \longrightarrow Me_2SO \longrightarrow Me_2S$.

Sodium ethanesulphonate and ethanesulphinate, dimethyl sulphoxide nitrate, and diethyl sulphone in well-grown cultures of *S. commune* gave no dialkyl sulphide. Probably therefore dimethyl sulphide arises by further methylation of the methylthiol.

It is possible that dimethyl disulphide is a primary product of *S. commune* and yields methylthiol on reduction, but this is uncertain. *S. commune* causes fission of dimethyl, diethyl, and di-*n*-butyl disulphides giving the corresponding thiols, and, in the first case, some dimethyl sulphide.

The traces of hydrogen sulphide evolved from *S. commune* cultures (see p. 424 and below) may arise by reduction of sulphate or thiosulphate to sulphide, a reaction effected by certain bacteria (see Stephenson, "Bacterial Metabolism", Longmans, 1930, 76; Ellis, "The Sulphur Bacteria", Longmans, 1931, 22), or possibly by fission of a disulphide, *e.g.*, MeS·SMe giving MeSH and MeSOH, the sulphenic acid giving formaldehyde and hydrogen sulphide by Schöberl's reaction (*Annalen*, 1933, **507**, 111; 1936, **522**, 97).

At one time it appeared possible that the methylthiol produced by *S. commune* might arise by fission of the C–SMe group of methionine, $SMe \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H$, synthesised by the fungus. Addition of *dl*-methionine to well-grown cultures of *S. commune*, however, gave only traces of methylthiol or dimethyl sulphide. When *dl*-methionine was present in a suitable medium from the outset as sole source of sulphur, some methylthiol and traces of hydrogen sulphide were evolved, but the amount was very slight in comparison with that obtained using the Birkinshaw medium (*loc. cit.*)

It seemed worth while to determine whether a similar stability would be exhibited by methionine in bread cultures of *S. brevicaulis*. Somewhat to our surprise the amino-acid was readily converted into methylthiol and dimethyl sulphide. With *S*-methyl-, *S*-ethyl- and S-*n*-propyl-cysteine under identical conditions, the corresponding alkylthiol and alkyl methyl sulphide were produced in each case. This fission of the C–S link may be reductive giving homoalanine as the other primary product, or hydrolytic giving homoserine,

$$CH_3(OH) \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H.$$

Methionine is converted by kidney or liver slices into the keto-acid, $SMe \cdot CH_2 \cdot CH_2 \cdot CO \cdot CO_2H$ (Borek and Waelsch, *J. Biol. Chem.*, 1941, **141**, 99) and on feeding to rats (Waelsch, *ibid.*, 1941, **140**, 313); see also Handler and Bernheim, *ibid.*, 1943, **150**, 335). The methionol, $SMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot OH$, isolated from soya sauce by Akabori and Kaneko (*Proc. Imp. Acad. Japan*, 1936, **12**, 131) doubtless arises from methionine. Akobe (*Z. physiol Chem.*, 1936, **244**, 14) states that with *O. lactis* and *l*-methionine small amounts of methylthiol and diethyl sulphide are formed, but gives no details of their detection or characterisation. No other record of the formation of methylthiol from methionine occurs in the literature, although the keto-acid yields methylthiol with hot acid or alkali (Waelsch and Borek, *J. Amer. Chem. Soc.*, 1939, **61**, 2252; see also Behagel and Ratz, *Ber.*, 1939, **72**, 1257; Nicolet, *J. Amer. Chem. Soc.*, 1931, **53**, 3066).

The thiols obtained in *S. brevicaulis* cultures from methionine and the *S*-alkylcysteines may therefore be formed from keto-acids rather than directly from the amino-acids themselves. The behaviour of other methylthiol derivatives of carboxylic acids is under investigation. Ethylthioacetic acid, $SEt \cdot CH_2 \cdot CO_2H$, yields neither ethylthiol nor methyl ethyl sulphide in bread cultures of *S. brevicaulis*.

Borek and Waelsch (*loc. cit.*) state that homocystine and homocysteine are not deaminised by tissue slices, and refer to "the formation of hydrogen sulphide from homocysteine as from cysteine (compare Smythe, *J. Biol. Chem.*, 1942, **142**, 387) by the action of tissue slices". This may possibly have a botanical significance. Allyl *iso*thiocyanate, a product of the hydrolysis of the glycoside sinigrin occurring in black mustard seeds, may be formed by elimination of hydrogen sulphide from homocysteine (arising from methionine) followed by decarboxylation and interaction of the resulting amine with hydrogen sulphide and carbon dioxide:

$$SH \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H \xrightarrow{-H_2S} CH_2{:}CH \cdot CH(NH_2) \cdot CO_2H \xrightarrow{-CO_2}$$

$$CH_2{:}CH \cdot CH_2 \cdot NH_2 \xrightarrow[+H_2S]{+CO_2} CH_2{:}CH \cdot CH_2 \cdot NCS + 2H_2O$$

The relation existing between the *iso*thiocyanates of the *Cruciferæ* (see Armstrong and

Armstrong, " The Glycosides ", Longmans, 1931, p. 66) and the corresponding amino-acids has been pointed out by Barger and Coyne (*Biochem. J.*, 1928, **22**, 1417) with reference to methionine and cheirolin, $SO_2Me{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NCS$, which occurs as the glycoside glucocheirolin in wall-flower seeds, and also for phenylethyl *iso*thiocyanate (from the glycoside gluconasturtiin, in the garden nasturtium) and phenylalanine.

The existence of erysolin, $SO_2Me{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NCS$ (found as glucoerysolin in the seeds of the bright orange wall-flower), suggests the advisability of a search for homomethionine among the products of protein hydrolysis.

Diallyl disulphide, which occurs in oil of garlic (Semmler, *Arch. Pharm.*, 1892, **230**, 434) and was isolated as an oxygenated derivative, probably $C_3H_5{\cdot}S{\cdot}S(\rightarrow O){\cdot}C_3H_5$, from the same source by Cavallito *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 1950, 1952; 1945, **67**, 1032), may also be formed from homocystine by loss of ammonia and carbon dioxide, a suggestion supported by the well-known enzymic equilibrium existing between fumaric and aspartic acids,

$$[CO_2H{\cdot}CH(NH_2){\cdot}CH_2{\cdot}CH_2{\cdot}S]_2 = 2CO_2 + 2NH_3 + (CH_2{:}CH{\cdot}CH_2{\cdot}S)_2.$$

The fission of the C–SMe link in methionine and the *S*-alkylcysteines has, we believe, only one biological counterpart, namely the fission of cystathionine,

$$CO_2H{\cdot}CH(NH_2){\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$$

(Brown and du Vigneaud, *J. Biol. Chem.*, 1941, **137**, 611; du Vigneaud, Brown, and Chandler, *ibid.*, 1942, **143**, 59). In presence of rat liver or its saline extracts or kidney slices, this gives cysteine and probably homoserine, $CH_2(OH){\cdot}CH_2{\cdot}CH(NH_2){\cdot}CO_2H$, or its phosphoric ester (Binkley, Anslow, and du Vigneaud, *ibid.*, p. 559; Binkley, *ibid.*, 1944, **155**, 39). This fission is probably reversible (Binkley and du Vigneaud, *ibid.*, 1942, **144**, 506), and cystathionine appears to play an important part in the biological conversion of methionine into cystine (Stetten, *ibid.*, p. 501; du Vigneaud *et al.*, *ibid.*, 1944, **155**, 650).

We find that methionine methiodide (Toennies and Kolb, *J. Amer. Chem. Soc.*, 1945, **67**, 849) gives dimethyl sulphide but no methylthiol in bread cultures of *S. brevicaulis*. Homoserine or α-aminovinylacetic acid may be the other product.

$$CO_2H{\cdot}CH(NH_2){\cdot}CH_2{\cdot}CH_2{\cdot}SMe_2\}X + H{\cdot}OH = Me_2S + HX + CO_2H{\cdot}CH(NH_2){\cdot}CH_2{\cdot}CH_2{\cdot}OH$$

This suggests that formation of a sulphonium derivative is not involved in the C–S fission of methionine discussed above. Trimethylsulphonium iodide yields no volatile sulphur compound under similar conditions.

Methyl β-methylthiopropionate, $SMe{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Me$ (*A*), occurs in pine-apple juice (Haagen-Smit *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 1651), and the chloride of *S*-dimethyl-β-propiothetine, $Me_2\overset{+}{S}(Cl^-){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, has been isolated from the red alga *Polysiphonia fastigiata* by Miss M. I. Simpson and one of us (forthcoming publication). This sulphonium chloride (*B*) (or other salt) is the precursor of the dimethyl sulphide shown by Haas (*Biochem. J.*, 1935, **29**, 1258) to be evolved by the alga. *A* and *B* may originate from either methionine or cystine, and the free base of *B* and the ester *A* may be biologically connected by a change analogous to the conversion of betaine into methyl dimethylaminoacetate (Willstätter, *Ber.*, 1902, **35**, 584). This comparison of a β-thetine with an α-betaine is put forward with reserve, because *B* with alkali gives dimethyl sulphide and acrylic acid (Holmberg, *Arkiv Kemi, Min. Geol.*, 1946, **21**, *B*, 1). (The liberation of dimethyl sulphide by the alga is probably a very similar reaction.) On the other hand, β-propiobetaine readily gives acrylic acid and trimethylamine, and does not undergo the isomeric change (Willstätter, *loc. cit.*, p. 611).

Experimental.

Growth of S. commune *on a Medium containing Sulphate. Formation of Dimethyl Sulphide and Methylthiol.*—Twenty 1-l. flasks each containing 300 c.c. of the medium used by Birkinshaw *et al.* [glucose (3%) in tap water, with $(NH_4)_2SO_4$ (0·3%), KH_2PO_4 (0·25%), $MgSO_4,7H_2O$ (0·1%), " Marmite " (0·01%), and traces of $FeCl_3$, $CuSO_4$, $MnSO_4$, $ZnSO_4$, and borax] were sterilised, inoculated with mycelium from a wort agar culture of *S. commune*, and incubated for 6 days at 32° and 3 days at room temperature. The flasks were arranged in four parallel sets of 5 in series, and volatile products aspirated through 4% aqueous mercuric cyanide and 3% aqueous mercuric chloride for 53 days. The deposits in the cyanide (3·81 g.) melted between 130° and 140°, and yielded mercury dithiomethoxide, m. p. 174°, on recrystallisation, not depressing the m. p. of an authentic specimen, m. p. 175°. The first and third contained traces of the yellow double compound $(MeS)_2Hg,2HgS$, but the second was white.

The deposits in the mercuric chloride (2·74 g.) melted between 143° and 147° (decomp.) but some from the bottles nearest the cultures were not completely fused at 260°. The deposits were treated with sodium hydroxide and volatile products aspirated through mercuric cyanide and chloride. No deposit formed in the cyanide but a white solid (0·02 g.) separated in the chloride during 24 hours. It had m. p. 157° and mixed m. p. 156—157° with authentic dimethyl sulphide mercurichloride of m. p. 157—158°. There was much less dimethyl sulphide than methylthiol.

In a second experiment the dimethyl sulphide was identified as before and also absorbed in alcoholic benzyl chloride giving benzyldimethylsulphonium picrate, m. p. 134°, and m. p. 133·5—134° in admixture with a specimen, m. p. 133·5—134° (see Baker and Moffitt, *J.*, 1930, 1722).

After removal of dimethyl sulphide from the crude mercurichloride the alkaline residue was acidified. Aspiration into mercuric cyanide gave mercury dithiomethoxide, m. p. and mixed m. p. 173—174°. The original deposits in the mercuric chloride therefore contained a derivative of methylthiol (MeSHgCl or MeSHgCl,xHgCl$_2$ or both). As no methylthiol escaped from the original mercuric cyanide tubes this must have arisen from dimethyl disulphide formed from methylthiol during aeration of the cultures. MeSHgCl is unmelted at 260° and preponderates if dimethyl disulphide in excess reacts with mercuric chloride. This probably explains the high m. p. of the deposits in the first two mercuric chloride tubes.

Evolution of Methylthiol from S. commune *Cultures on Breadcrumbs containing no Added Substrate.*—Five 1-l. flasks each containing 150 g. of bread and 25 c.c. of water were sterilised, inoculated with *S. commune*, and incubated at 32°. An odour developed in 3—6 days, so the flasks were connected in series and sterile air drawn through into mercuric cyanide and chloride. In the cyanide a yellow deposit formed which, after recrystallisation from ethyl acetate (to remove Hg(SMe)$_2$,2HgS), gave mercury dithiomethoxide, m. p. 175°. The slight deposit in the chloride melted at 150—153° and at 140—145° in admixture with dimethyl sulphide mercurichloride (m. p. 157°). It gave an odour of dimethyl sulphide with sodium hydroxide but consisted mainly of MeSHgCl,xHgCl$_2$. With hydrochloric acid it gave an odour of methylthiol. A second experiment gave a similar result.

Formation of Pyruvic Acid by S. commune *on a Synthetic Medium containing Glucose.*—The fungus was grown on Birkinshaw's medium (see p. 426) for 3 months. 600 C.c. were then concentrated and treated with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The yellow precipitate (0·2 g.), m. p. 210—212° (decomp.), was completely soluble in aqueous sodium carbonate and was reprecipitated by acid, unchanged in m. p. Recrystallisation from alcohol gave orange-yellow crystals, m. p. 216—217°, not depressing the m. p. of pyruvic acid 2 : 4-dinitrophenylhydrazone (m. p. 218°).

With *p*-nitrophenylhydrazine a similar procedure (800 c.c.) gave an orange solid (0·2 g.) which on crystallisation from alcohol–ether had m. p. 219—220° (decomp.) alone and in admixture with pyruvic acid *p*-nitrophenylhydrazone [m. p. 220—222° (decomp.)].

No inorganic sulphide, cystine, or cysteine could be detected in the medium. Extraction with chloroform yielded no dialkyl sulphone.

S. commune *and Diethyl Disulphide.*—Four 1-l. flasks each containing 200 c.c. of wort were inoculated with *S. commune*. After 10 days evolution of methylthiol (see above) had ceased. Each flask then received 25 c.c. of a 2% aqueous suspension of carefully purified diethyl disulphide. After 24 hours, aspiration into mercuric cyanide and chloride was begun. Deposits in the cyanide of m. p. range 70° to 76°, sintering at 60°, were obtained. Recrystallisation from alcohol gave mercury dithioethoxide, m. p. 73° and mixed m. p. 74—75° with a specimen of m. p. 74—75°. Later, traces of mercuric sulphide formed in the cyanide solution. The first two mercuric chloride tubes contained deposits which were unmelted at 260° owing to the presence of EtSHgCl formed from the disulphide (see p. 424).

The deposit from the fourth mercuric chloride tube did not depress the m. p. (151°) of an authentic specimen of EtSHgCl,HgCl$_2$, but was not quite pure. It gave ethylthiol with hydrochloric acid, but with sodium hydroxide gave a distinct odour of an alkyl sulphide (cf. Challenger and Rawlings, *J.*, 1937, 872). Extraction with benzene yielded no methyl ethyl sulphide mercurichloride, however, and EtSHgCl,HgCl$_2$ remained insoluble.

In a second experiment with 6 cultures, deposits in the mercuric chloride were treated with sodium hydroxide. Aspiration through mercuric chloride (see p. 426) gave negative results.

S. commune and *Di-n-butyl Disulphide.*—Four 1-l. flasks (200 c.c. of sterile wort) were inoculated and incubated for 12 days at 32° and six days at room temperature. Each then received 25 c.c. of a 2% suspension of di-*n*-butyl disulphide. Aspiration as usual after 36 hours yielded a deposit (0·9 g.) in the mercuric cyanide which, after two crystallisations from alcohol to remove traces of mercuric sulphide, had m. p. 82—83° alone and 83—84° in admixture with mercury di-*n*-thiobutoxide (m. p. 84—85°).

Deposits in the mercuric chloride after 30 days had m. p. 177° unchanged by admixture with chloromercuri-*n*-thiobutoxide, BuSHgCl, and doubtless arose by fission of di-*n*-butyl disulphide. On examination it was clear that only traces of the mercurichloride of methyl *n*-butyl sulphide were present.

S. commune *and Dimethyl Disulphide.*—The disulphide, prepared by Stutz and Schriner's method (*J. Amer. Chem. Soc.*, 1933, **55**, 1242), was free from methylthiol and hydrogen sulphide.

Five wort cultures of *S. commune*, grown for 6 days at 32° and 3 days at room temperature, received 25 c.c. of a sterile 2% aqueous suspension of the disulphide. Aspiration through mercuric cyanide and chloride yielded, after 5 days, 3·7 g. of mercury dithiomethoxide, m. p. 174—175°, containing traces of yellow (MeS)$_2$Hg,2HgS. The deposits in the chloride were treated with sodium hydroxide. Aeration through mercuric chloride gave dimethyl sulphide mercurichloride, m. p. and mixed m. p. 157—158°.

Blank experiment. About 6·5 g. of the dimethyl disulphide were mixed with excess of aqueous mercuric chloride, and the MeSHgCl,xHgCl$_2$ was separated and treated with sodium hydroxide. Aspiration through aqueous mercuric chloride gave no precipitate, indicating the complete absence of dimethyl sulphide.

S. commune *and Sodium Selenate.*—Four 1-l. flasks each containing 200 c.c. of sterile wort were inoculated and incubated for 10 days at 32° and 17 days at room temperature. Addition to each of 25 c.c. of a sterile 0·7% sodium selenate solution and aspiration through Biginelli's solution (*J.*, 1933, 98) gave, after 22 days, 0·01 g. of solid, m. p. 154° and mixed m. p. 152° with dimethyl selenide mercurichloride of m. p. 153° (all with decomp.). Using 25 c.c. of a 2·4% solution of sodium selenate, growth was partly inhibited.

Behaviour of Sodium Sulphite and Sulphate in developing Cultures of S. commune *on Wort.*—In an attempt to compare the ease of methylation of sulphite and sulphate by *S. commune* the fungus was grown on sterile wort. Suitable quantities (about 0·25%) of sodium sulphate and sulphite were added on cessation of the evolution of methylthiol (10 days). Aspiration into mercuric cyanide and chloride gave only a faint yellow turbidity during 30 days.

Possibly, therefore, the methylation of inorganic sulphate may be associated with the early stages of the growth of the fungus. In view of the very slight formation of methylthiol (see p. 425) on addition of *dl*-methionine to established cultures of the organism, the experiment was repeated with methionine present from the outset.

Growth of S. commune *on a Medium containing Glucose with* dl-*Methionine as Sole Source of Sulphur.*—An aqueous medium was made up containing glucose (3%), NH_4NO_3 (0·3%), KH_2PO_4 (0·25%), $MgCl_2$ (0·1%), and *dl*-methionine (0·2%). This corresponded to the medium used on p. 426 with addition of NO_3', Cl′ and methionine, and omission of SO_4'', the " trace elements ", and " marmite ".

Four 1-l. flasks each containing 200 c.c. of sterile medium were inoculated with *S. commune*. The flasks were placed in an incubator at 32° and immediately connected in series, and a stream of sterile air was passed through them and into mercuric cyanide and chloride. After about 5 days at 32° a yellow deposit formed in the first cyanide tube but only increased slowly. It was removed after 28 days, weighed 0·10 g., and consisted of mercury dithiomethoxide and traces of its double compound with mercuric sulphide.

Even after 28 days at 32° the mould growth was scanty. No deposit formed in the mercuric chloride.

S. brevicaulis *and* dl-*Methionine.*—Five 250-c.c. flasks each containing 50 g. of sterile bread were inoculated with *S. brevicaulis* (Strain Washington 2, see *J.*, 1933, 98) and incubated for 4 days at 32° and one day at room temperature. 10 C.c. of a 2% solution of *dl*-methionine in sterile water were added to each flask (concn. in the bread = 0·4%), and the whole was connected in series and sterile air passed through into aqueous mercuric cyanide and chloride. After 7 days the white deposit in the cyanide when recrystallised from ethyl acetate had m. p. and mixed m. p. 174—175° with mercury dithiomethoxide of m. p. 175° (all with decomp.).

The deposits in the mercuric chloride on recrystallisation from benzene had m. p. and mixed m. p. 158° with dimethyl sulphide mercurichloride of m. p. 158°, and gave a strong odour of the sulphide with sodium hydroxide.

Control experiments. (*a*) Four 1-l. flasks each containing 250 g. of sterile bread were inoculated with the same strain of *S. brevicaulis* and incubated for 4 days at 32° and 2 days at room temperature. On aspiration through mercuric cyanide and chloride, except for a very faint trace of deposit in the first cyanide tube on the 4th day (disappearing later) there was no deposit in any tube during 23 days, and no odour.

(*b*) 10 C.c. of a 1% solution of methionine in sterile water were added to each of 4 flasks each containing 50 g. of sterile bread. Aspiration as before gave no deposit during 26 days.

S. brevicaulis *and* S-*Methylcysteine.*—This was prepared by du Vigneaud's method (*J. Biol. Chem.*, 1933, **101**, 719) and purified by repeated solution in water and precipitation with excess of alcohol, giving a specimen of constant m. p. 233° (uncorr.) on 3 successive precipitations [du Vigneaud *et al.* (*loc. cit.*) give m. p. 248° (decomp.) after sintering at 240°] (Found: C, 35·6; H, 6·7; S, 23·3, 23·5. Calc.: C, 35·5; H, 6·7; S, 23·7%).

20 C.c. of a solution of *S*-methylcysteine (0·71 g.) in sterile water (80 c.c.) were added to each of 4 bread cultures (250 g. of bread in 1-l. flasks; concn. in bread = 0·07%) which had been grown for 4 days at 32° and 4 at room temperature. On aspiration, deposits formed in the mercuric cyanide and chloride within a few hours and steadily increased during 25 days. Two deposits, about 0·35 g. in all, from the cyanide after recrystallisation from ethyl acetate had m. p. 175° and 173—174° and mixed m. p. 174—175° and 173—174° with mercury dithiomethoxide of m. p. 174° (all decomp.). Precipitates were obtained from the mercuric chloride of m. p. 147—148°, 151—152°, 135—140°. On crystallisation from benzene the m. p. and mixed m. p. was 157—158° with dimethyl sulphide mercurichloride of m. p. 157—158°. Traces of $MeSHgCl,xHgCl_2$ were present as evidenced by the small amount of residue insoluble in benzene.

S. brevicaulis *and* S-*Ethylcysteine.*—A specimen of *S*-ethylcysteine of m. p. 245—247° (Clark and Inouye, *J. Biol. Chem.*, 1931, **94**, 548) was recrystallised thrice from hot water by addition of alcohol. The four specimens when immersed in a bath at 150° all melted simultaneously at 245—246°, after sintering at 243—244°. That used for the experiment had the same m. p. (Found: C, 40·6; H, 7·4; S, 21·8. Calc.: C, 40·2; H, 7·4; S, 21·5%).

The cultures were as before and were incubated for 4 days at 32° and 3 days at room temperature. To each were added 25 c.c. of a 1% solution of *S*-ethylcysteine in sterile water (concn. in bread = 0·1%). Aspiration during 14 days yielded deposits in the cyanide (0·15 g.) which after two recrystallisations from alcohol had m. p. 76—77° and mixed m. p. 76—77° with mercury dithioethoxide of m. p. 75—76°. Deposits in the mercuric chloride of m. p. 127—128° and 125—127°, after crystallisation from acetone–light petroleum and benzene respectively had m. p. 127—128° and 126—127° not depressing the m. p. (127—128°) of methyl ethyl sulphide dimercurichloride.

Control experiment. 10 C.c. of a 1% solution of *S*-ethylcysteine in sterile water were added to each of four flasks each containing 250 g. of sterile bread. Aspiration into mercuric cyanide and chloride gave no deposits during 14 days.

S. brevicaulis *and* S-n-*Propylcysteine.*—*S-n*-Propylcysteine seems to be new. It was prepared from *l*-cystine as described by du Vigneaud (*loc. cit.*) for the *S*-methyl derivative. The crude product was repeatedly recrystallised from hot water, by addition of alcohol. The main *product* was then twice recrystallised and had a constant m. p. 244—245° (decomp.) (Found: C, 43·8; H, 7·6; S, 19·8. $C_6H_{13}O_2NS$ requires C, 44·1; H, 8·0; S, 19·6%).

Four bread cultures of the Washington strain of the mould were grown for 2 days at 32° and 12 days at room temperature. 25 C.c. of a solution of 0·53 g. of *S-n*-propylcysteine in sterile distilled water (100 c.c.) were added to each flask (concn. = 0·05%). During 4 weeks five deposits (0·28 g. in all) from the mercuric chloride all melted between 163° and 165° and did not depress the m. p. of methyl *n*-propyl sulphide mercurichloride (m. p. 163—164·5°). A grey deposit (0·05 g.) from the cyanide tubes, after recrystallisation from alcohol, had m. p. and mixed m. p. 67—68° with mercury di-*n*-thiopropoxide of m. p. 66—67°.

Other Moulds and dl-*Methionine.*—Bread cultures of *Penicillium notatum* and *P. chrysogenum*

(National Collection of Type Cultures Nos. 4222 and 589), of *P. notatum* var. (Bird and Challenger *J.*, 1939, 163) and of *Aspergillus niger* (strains " W 17 " and " 17 " kindly supplied by Dr. T. K. Walker, College of Technology, Manchester) containing 0·1% of *dl*-methionine gave no methylthiol or sulphide on aeration through mercuric cyanide and chloride for 3—4 weeks. With 0·5% of *dl*-methionine the first two moulds and *A. niger* " W 17 " gave faint odours resembling a thiol.

S. brevicaulis *and Homocystine, Cystine, and Cysteine.*—25 C.c. of a 1·2% solution of (*a*) homocystine and (*b*) cystine in sterile sodium carbonate (1%) and 25 c.c. of a 2% solution of cysteine in sterile water were added to 3 bread cultures in each case. No odour was produced and no deposit formed on aspiration for 30 days through mercuric cyanide and chloride.

S. brevicaulis *and* dl-*Methionine Methiodide.*—The iodide was prepared by the method of Toennies and Kolb (*loc. cit.*) (see p. 426) who give m. p. about 155° (decomp.). Our specimen melted at 165° (decomp.) and was unaffected by a further crystallisation (Found : C, 25·1; H, 5·0; I, 43·7. Calc. for $C_6H_{14}O_2NIS$: C, 24·7; H, 4·8; I, 43·6%).

Six cultures (50 g. of bread) were grown for 6 days at 32° and 2 days at room temperature. 10 C.c. of a solution of the methiodide (1·0 g.) in sterile water (60 c.c.) were added to each flask, and volatile products aspirated through mercuric cyanide and chloride. During 30 days deposits (0·51 g. in all) were removed from the chloride tubes. On crystallisation from benzene the m. p. and mixed m. p. with dimethyl sulphide mercurichloride of identical m. p. was 157—158°. No deposit formed in the cyanide during this time.

Control experiment. 10 C.c. of a solution of the methiodide (0·6 g.) in sterile water (40 c.c.) were added to each of four flasks containing 50 g. of sterile bread. Aspiration through mercuric cyanide and chloride for 32 days produced no deposit.

The authors thank the Royal Society and Imperial Chemical Industries Ltd. for grants, and Dr. C. Harington, F.R.S., for a gift of *dl*-methionine.

THE UNIVERSITY, LEEDS, 2. [*Received, July 10th,* 1946.]

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85. *The Action of Heat on Diphenylchloroarsine.*

By G. D. PARKES, R. J. CLARKE, and B. H. THEWLIS.

The disproportionation of diphenylchloroarsine on heating has been investigated and the existence of an equilibrium at various temperatures above 200° has been established. No disproportionation takes place below 200° and diphenylchloroarsine can be distilled unchanged below that temperature. Evidence is brought forward to show that two equilibria are operating simultaneously at temperatures from 215° to 325°, *viz.*,

$$2AsPh_2Cl \rightleftharpoons AsPhCl_2 + AsPh_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

$$\text{and } AsPh_2Cl + AsPhCl_2 \rightleftharpoons AsPh_3 + AsCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

DIPHENYLCHLOROARSINE is known to undergo disproportionation on heating, and, since distillation is a stage in some methods which would otherwise be more convenient on a manufacturing scale, the conditions under which disproportionation takes place have been investigated.

The main reaction which occurs when diphenylchloroarsine is heated is (i); but since Pope and Turner (*J.*, 1920, **117**, 1447) obtained 80% yields of diphenylchloroarsine by heating phenyldichloroarsine with triphenylarsine at 300° it appears probable that the reaction is reversible and that an equilibrium could be set up. Hence the composition of the equilibrium mixture and the length of time required for the establishment of equilibrium at various temperatures has been investigated by heating quantities of about 1 g. of diphenylchloroarsine and of an equimolecular mixture of phenyldichloroarsine and triphenylarsine in a pair of similar sealed tubes in an electrically heated air-bath for varying times at known temperatures. The composition of the product was then determined by estimating the quantity of triphenylarsine present by precipitation with mercuric chloride, which La Coste and Michaelis (*Annalen*, 1880, **201**, 242) used as a qualitative reagent for the separation of triphenylarsine from diphenylchloroarsine. It has now been shown that this reagent can be used quantitatively and the necessary technique devised. The possibility of using mercuric iodide similarly was investigated, but this reagent was found to be unsuitable. The process was repeated using successively longer times of heating until both tubes were found to contain the same amount of triphenylarsine per g. of diphenylchloroarsine (or of the equimolecular mixture of phenyldichloroarsine and triphenylarsine) taken. It could then be taken for certain that equilibrium had been established. This was done at 200°, 230°, 250°, 275°, 290°, 300°, and 315°. At the lower temperatures equilibrium was only slowly established; in fact, below 220° the reaction was so slow that it was impracticable to heat long enough for an equilibrium to be reached : several days' heating would probably have been needed. At 300°, however, equilibrium was much more rapidly established, no further change being observed after one hour in the case of

diphenylchloroarsine. But the triphenylarsine–phenyldichloroarsine mixture still required about three hours for the attainment of equilibrium, even at 300°.

Experimental.

Mercuric Chloride Solution as a Quantitative Reagent for Triphenylarsine (cf. La Coste and Michælis, *loc. cit.*).—After many experiments the following procedure was found satisfactory for the estimation of triphenylarsine. The mixture of phenyldichloroarsine, diphenylchloroarsine, and triphenylarsine, obtained by heating diphenylchloroarsine, the triphenylarsine content of which it is desired to determine, is dissolved in 25 c.c. of pure alcohol and treated with 20 c.c. of an alcoholic mercuric chloride solution (10 g. in 200 c.c. of alcohol). The solution is stirred and left for about 15 minutes (if left for longer than this, a precipitate is formed, possibly of $AsPh_2O{\cdot}OHg$, which might be confused with $AsPh_3,HgCl_2$). It is then filtered through a weighed Gooch crucible, washed with 50 c.c. of alcohol, dried at 100° in a steam-oven, and weighed. The following results of test estimations indicate the degree of accuracy attainable.

Mixture.			Triphenylarsine found by above process (g.).
Phenyldichloroarsine (g.).	Diphenylchloroarsine (g.).	Triphenylarsine (g.).	
—	0·5632	0·3014	0·2968
—	0·7113	0·1418	0·1397
0·2493	0·5141	0·3101	0·2991
0·3027	0·6002	0·3279	0·3198

Action of Heat on Diphenylchloroarsine.—Vertical, cylindrical, electrically-heated air-baths (about 30 cm. high and 8 cm. in diameter) were used, the temperature of which could be varied between 200° and 320°. Each air-bath was fitted with a lid carrying a thermometer and four vertical test-tubes, in which sealed up tubes containing diphenylchloroarsine (or a mixture of phenyldichloroarsine and triphenylarsine) could be placed. Any one or all of the four sealed tubes could be removed after heating, and cooled rapidly to room temperature, thus freezing the equilibrium. About 1 g. of diphenylchloroarsine was weighed into a glass tube sealed at one end, which was then sealed. The equimolecular mixture of phenyldichloroarsine and triphenylarsine was weighed out into another similar tube, which was also sealed. A solution of exactly equimolecular amounts of phenyldichloroarsine and triphenylarsine in ether was prepared, containing 12·2360 g. of triphenylarsine and 8·9120 g. of phenyldichloroarsine, in 100 c.c. Portions of 5 c.c. were transferred to a tube sealed at one end. This was then gently heated electrically to remove ether, leaving a mixture of exactly equimolecular amounts of phenyldichloroarsine and triphenylarsine. The temperature of the vessel was never allowed to rise above 100°, at which temperature no reaction between the phenyldichloroarsine and triphenylarsine takes place. The tube was then sealed and heated in the air-bath. Four tubes prepared in this way were simultaneously heated to 300° for 1 hour; the contents on analysis gave respectively the following amounts of triphenylarsine per g. of mixture: 0·2091, 0·2090, 0·2093, 0·2095. Since these values are sensibly the same as those of 0·2089 and 0·2090 obtained in another experiment, in which the phenyldichloroarsine and triphenylarsine were weighed out into tubes, it is seen that the possible presence of traces of ether in triphenylarsine–phenyldichloroarsine mixtures obtained by the above process has no effect on the reaction taking place.

The following table gives the results obtained for temperatures between 200° and 320°.

t.	*a.*	*b.*	*t.*	*a.*	*b.*	*t.*	*a.*	*b.*
Temperature, 200°.			Temperature, 230° (*contd.*).			Temperature, 290°.		
1	0·5786	0·0007	4	0·2783	0·0953	1	0·3026	0·1509
2	0·5785	0·0008	5	0·2249	0·1092	2	0·2437	0·1637
3	0·5780	0·0010	6	0·1853	0·1237	3	0·2095	0·1731
			7	0·1589	0·1347	4	0·1833	0·1802
Temperature, 215°.			8	0·1390	0·1392	5	0·1809	0·1806
1	0·5786	0·0030				Temperature, 300°.		
3	0·5701	0·0095	Temperature, 250°.			½	—	0·1356
5	0·5602	0·0319	1	0·4860	0·1179	1	0·2091	0·1519
6	0·5509	0·0457	2	0·3791	0·1280	2	0·1735	0·1513
7	0·5405	0·0683	3	0·2690	0·1362	3	0·1513	0·1510
8	0·5297	0·0816	4	0·1437	0·1422	4	0·1510	0·1509
9	0·5183	0·1073	5	0·1420	0·1420			
						Temperature, 320°.		
Temperature, 230°.			Temperature, 275°.			¼	—	0·1253
1	0·4890	0·0510	1	0·4910	0·1372	¾	—	0·1709
2	0·4087	0·0673	2	0·3400	0·1498	1	0·2001	0·1637
3	0·3326	0·0801	3	0·2398	0·1537	2	0·1647	0·1375
			4	0·1679	0·1670	3	0·1339	0·1158
			5	0·1670	0·1671	4	0·1166	0·1009
						5	0·1010	0·0998

t = Time of heating (hours).
a = Weight (g.) of triphenylarsine left from 1 g. of phenyldichloroarsine–triphenylarsine.
b = Weight (g.) of triphenylarsine formed from 1 g. of diphenylchloroarsine.

Since practically no triphenylarsine was produced on heating diphenylchloroarsine at 200°, it seemed likely that distillation under reduced pressure, at or below this temperature, might be possible without any decomposition taking place. This was found to be so. Diphenylchloroarsine was distilled (b. p. 193°/20 mm.) and a portion of the distillate was dissolved in alcohol and treated with mercuric chloride solution. No precipitate was observed, indicating that no decomposition with formation of triphenylarsine had occurred under these conditions. As a result of this work it may be concluded that:

(1) No marked disproportionation of diphenylchloroarsine takes place at, or below, 200°. Hence diphenylchloroarsine can be distilled without decomposition below this temperature.

(2) Disproportionation is only very slow below 215°.

(3) A definite equilibrium exists which, if represented by equation (i), moves to the right as the temperature is raised to about 285° (after which it moves to the left again). This might be due to a change in the sign of the heat of reaction, but this is improbable. It is more probably due to the reaction being more complex than was at first thought, the relative speeds of the different reactions involved changing with temperature. This conclusion is also supported by the fact that at temperatures up to 300° the amount of triphenylarsine formed on heating diphenylchloroarsine increases with time until equilibrium is reached. But at 320° the amount of triphenylarsine formed by heating diphenylchloroarsine increases rapidly during the first ¾ hour and then *falls* to the equilibrium value during the next 3 hours.

Since diphenylchloroarsine was obtained by Michaelis (*Annalen*, 1902, **320**, 271; **321**, 141) by heating triphenylarsine with arsenic trichloride, a probable further reaction is $AsPh_2Cl + AsPhCl_2 = AsPh_3 + AsCl_3$. If this be so, it is likely that arsenic trichloride would be present in the equilibrium mixture, and a qualitative test for it was therefore made. Diphenylchloroarsine was heated for two hours at 315°, allowed to cool, and treated with water to convert any arsenic trichloride present to arsenious acid, the other arsenicals forming an insoluble residue. The liquid was acidified with hydrochloric acid and treated with hydrogen sulphide. A slight yellow precipitate was observed. The neutral solution similarly gave a brown precipitate with silver nitrate. Hence a small amount of arsenic trichloride is present in the reaction mixture. It would seem likely therefore that when diphenylchloroarsine is heated reactions (i) and (ii) take place simultaneously.

DYSON PERRINS LABORATORY, OXFORD. [*Received, July 10th*, 1946.]

NOTE.

Note on the Chlorination of 2-Aminothiazole with Sulphuryl Chloride. By E. PEDLEY.

2-ACETAMIDOTHIAZOLE is chlorinated by the action of sulphuryl chloride to give the 5-chloro-compound, hydrolysed to 5-chloro-2-aminothiazole identical with that described by English, Clarke, Clapp, and Ebel (*J. Amer. Chem. Soc.*, 1946, **68**, 453).

2-Acetamidothiazole. 50 G. of 2-aminothiazole were added in portions, with thorough shaking, to 150 g. of acetic anhydride. The solid obtained was melted, boiled under reflux for ½ hour, and poured into 500 ml. of water. The precipitated acetyl derivative on recrystallisation from water (charcoal) gave white, matted, needle-shaped crystals (35 g.), m. p. 203° (Found: N, 19·5. Calc. for $C_5H_6ON_2S$: N, 19·7%).

5-Chloro-2-acetamidothiazole. 50 G. of the above compound were suspended in 500 ml. of dry carbon disulphide and heated under reflux during the slow addition of 50 g. of sulphuryl chloride mixed with 100 ml. of carbon disulphide (vigorous stirring) and for ½ hour thereafter. The crystals which separated on cooling were filtered off, washed thoroughly with carbon disulphide, and dried in air. Recrystallisation from alcohol yielded 25 g. of white needles, m. p. 208° (Found: N, 15·7. Calc. for $C_5H_5ON_2ClS$: N, 15·9%), undepressed on admixture with the acetyl derivative of 5-chloro-2-aminothiazole obtained according to English *et al.* (*loc. cit.*).

5-Chloro-2-aminothiazole. 5 G. of the foregoing acetyl compound were boiled for 20 minutes under reflux with 50 ml. of 10% hydrochloric acid, and then for 5 minutes with addition of charcoal. The filtered and cooled solution was basified by sodium carbonate, and the precipitated base extracted with ether. The extract was dried (K_2CO_3), filtered, and then passed through a short column of chromatographic aluminium oxide. Removal of the solvent yielded a creamy white solid, m. p. 111° (Found: N, 20·2. Calc. for $C_3H_3N_2ClS$: N, 20·8%), undepressed on admixture with a specimen (m. p. 111°) from dichloroacetal and thiourea.—MESSRS. J. WOOLLEY SONS & CO. LTD., MANCHESTER. [*Received, July 3rd*, 1946.]

OBITUARY NOTICES.

JOSEPH JOHN BLACKIE.

1895—1946.

THE sudden death on October 30th of Joseph John Blackie removed a chemist of great eminence in pharmaceutical circles, who was keenly interested in the progress of research. A native of Duns, Berwickshire, he served his apprenticeship there, and qualified in pharmacy in 1920. Blackie saw service in the First World War as Sergeant and Staff-Sergeant in the Royal Army Medical Corps in Gallipoli, Egypt, and France, and then joined the staff of Duncan Flockhart & Co. as assistant laboratory manager. In 1922 he secured the Ph.C. qualification, was appointed laboratory manager in 1924, and in 1930 became a partner in the firm he had joined ten years previously, and with which he was associated throughout his working life. Blackie's responsibilities now involved the control of the research and manufacturing side of the business in Edinburgh, but this did not deter him from joining the very active research school of the late Professor George Barger, F.R.S. Here his wide botanical knowledge and manipulative skill served him in good stead in an investigation of the alkaloids of the genus *Senecio*, for which the University of Edinburgh awarded him the degree of Ph.D. in 1935. Together with Barger, Blackie used to scour the countryside for the raw material for his researches, with great pleasure and profit to both collaborators (*J.*, 1936, 743; 1937, 584).

Dr. Blackie was admitted a member of the Edinburgh Merchant Company in 1932 and elected a governor of the Heriot-Watt College in 1934, a Fellow of the Royal Institute of Chemistry in 1936, and a Fellow of the Royal Society of Edinburgh in 1937. He played a great part in the affairs of the North British Branch of the Pharmaceutical Society of Great Britain, having been appointed to the Board of Examiners for Scotland in 1925; he was serving as Chairman of the Board at the time of his death, having held that office since January 1938. In his examining, and in the Chair, Blackie, although he would never tolerate any lowering of standards, always had the interests of the candidates at heart, and the author of this notice recalls with great pleasure the happy times spent as a co-examiner in his company.

The onset of war in 1939 greatly increased Blackie's responsibilities owing to the depletion of his staff, the increased demand for anæsthetics, and the vulnerability of the works from the viewpoint of fire risks, and he worked untiringly throughout the whole period. It is to be feared that his refusal to take even the briefest of holidays played no inconsiderable part in hastening his untimely death. A man of the highest character and ability, his unassuming and kindly disposition brought him many friends who deeply mourn his loss at the height of his powers.

E. G. V. PERCIVAL.

ROBERT SELBY MORRELL.

1867—1946.

ROBERT SELBY MORRELL was born on August 20th, 1867, at Manningham, Bradford, and attended Bradford Grammar School. In 1886 he went to Gonville and Caius College, Cambridge, graduated in 1890, received his M.A. degree in 1894, and became a Fellow of his college in 1896, which status he retained until 1904. Between 1890 and 1893 he was at Wurzburg and received the Ph.D. degree.

In 1904 Morrell joined the staff of Messrs. Mander Bros. Ltd., the well-known and old-established firm of paint and varnish manufacturers at Wolverhampton, as Chief Chemist, which position he retained until 1930. In the early years of the century he published some papers concerned with the oxidation of carbohydrates, but the move to Wolverhampton changed the whole course of his future work.

A scholar, a first-class chemist trained in the classical manner, an industrious and capable experimenter, he chose the difficult path of drying-oil chemistry, convinced of its scientific importance and confident that a strictly scientific approach to problems of industrial and technical interest would be rewarded. Thus began many years of accurate and painstaking work and constant breaking of new ground, in a field in which he stood for years, at least as far as this country was concerned, practically alone.

The scientific literature, notably the *Journal* of the Chemical Society, contains a wealth of papers, bearing his name, on drying-oil chemistry. In later years he concentrated mainly on

the problem of the mechanism of autoxidation and polymerisation of drying oils, particularly tung oil, from which he prepared derivatives in pure form suitable for experimental study. He stressed continually the differences in reactivity of the three double bonds of the elæostearic acid molecule and finally cleared the ground with the different maleic anhydride adducts of α- and β-elæostearic acid, which he isolated and characterised; he concluded that in the α-compound the double bond near to the carboxyl group remained free, and in the β-compound, the bond remote from the carboxyl. These adducts prepared by Morrell were used by Rideal for the first studies of the autoxidation of drying oils by the surface film technique.

Three text books which he wrote " Varnishes and their Components ", " The Chemistry of Drying Oils " (with H. R. Wood), and " Rubber, Resins, Paints & Varnishes " (with A. de Waele) are still standard works, and it should not be forgotten that they were produced at a time when such books were scarce. More recently, he edited " The Chemistry of Natural and Synthetic Resins " and " Synthetic Resins and Allied Plastics ".

Morrell took a wide interest in art and artists and lectured on the Chemistry of Artists' Materials in London over the period 1931—1937; these lectures were published in book form in 1939. He also contributed the section upon Drying Oils for the *Annual Reports on the Progress of Applied Chemistry*.

Morrell was a prominent figure in the early days of the Oil and Colour Chemists' Association and was President during 1920 and 1921, in which office he succeeded Mollwo Perkin.

During the period 1920—1926, Morrell lent all his aid to the thesis that the obviously developing need of research in the paint and varnish industry must be met; when the Research Association of British Paint, Colour and Varnish Manufacturers was formed in 1926 he was a staunch supporter and gave freely of his knowledge and experience as a member of Council.

Throughout his life Morrell was an enthusiastic worker in what would be now called " further education ". In his Cambridge days he lectured under the auspices of the Kent County Council and later for the Workers' Educational Association. For many years he and his wife, who died in July 1946, served the Wolverhampton centre of the Oxford University Extension Lectures as treasurer and secretary respectively.

He was a President of the Wolverhampton branch of the Historical Association, a member for 25 years of the Wolverhampton Rotary Club, and a co-opted member of the Corporation Art Gallery and Public Library Committee.

He was a staunch Churchman and a greatly admired and loved member of the community of Tettenhall Wood where he lived for thirty-five years. His friends and associates in a wider field also remember him as a rich and lovable personality who used his gifts freely and unsparingly in the service of all who called upon him.

L. A. JORDAN.

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